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Health Issue Assessment

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Health Issue Assessment

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This report reviews and evaluates the scientific information on the potential health effects from mercury exposure, with emphasis on those effects associated with human chronic inhalation exposures. The findings are based on a review of the scientific literature since the promulgation of the 1973 National Emission Standard for Mercury.

This report consists of six chapters that provide a cohesive discussion of all aspects of mercury exposure and focus upon those data thought to be most useful and relevant for human health risk assessment purposes.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
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PREFACE

The Office of Health and Environmental Assessment, in consultation with other Agency and non-Agency scientists, has prepared this mercury health effects update at the request of the Office of Air Quality Planning and Standards.

In the development of this report, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared such that the toxicity of mercury is qualitatively and, where possible, quantitatively identified. Observed effect levels and dose-response relationships are discussed where appropriate in order to place significant health responses in perspective with observed environmental levels.

ABSTRACT

Mercury is unique amongst the metals as being the only metal in a liquid form at room temperature. It exists in three oxidative states--metallic (Hg°), mercurous (Hg_2^{++}), and mercuric (Hg^{++}) mercury--and a wide variety of chemical forms, the most important being compounds of methyl mercury, mercuric mercury, and the vapor of metallic mercury. The global cycle of mercury involves the emission of Hg° from land and water surfaces to the atmosphere, transport of Hg° in the atmosphere on a widespread basis, possible conversion to unidentified soluble species and return to land and water of various depositional processes. The major source of human exposure to mercury (methyl mercury) is via the diet, through the consumption of fish and fish products.

Uptake of mercury vapor is through inhalation, whereas uptake of inorganic and methyl mercury compounds is primarily through oral ingestion. Once absorbed, mercury in all forms is distributed via the bloodstream to all tissues in the body; however, in the case of methyl mercury, tissue distribution is more uniform. Mercury vapor and methyl mercury readily cross the blood-brain and placental barriers.

Chronic exposures to mercury compounds primarily affect the central nervous system and kidneys. Depending upon the form of mercury and level of intake, effects on the adult nervous system can range from reversible paresthesias and malaise to irreversible destruction of neurons in the cerebellar and visual cortices, leading to permanent signs of ataxia and constriction of the visual field. Prenatal life is the most sensitive stage of the life cycle to methyl mercury poisoning, with effects in infants ranging from psychomotor retardation to a severe form of cerebral palsy. All prenatal effects to date have been found to be irreversible.

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1. INTRODUCTION

The purpose of this report is to review and evaluate the scientific information on the potential health effects from mercury exposure, with particular emphasis placed on those effects associated with human chronic inhalation exposures. The findings of this report are based mainly on a review of the scientific literature published since the promulgation of the 1973 National Emission Standard for Mercury. However, literature published prior to 1973 has also been evaluated if deemed relevant to the assessment of human health risks from airborne mercury.

This report is organized into chapters which provide a cohesive discussion of all aspects of mercury exposure and delineate a logical linking of this information to human health risks. The chapters include: an executive summary (Chapter 2), which compares and contrasts the information of the past ten years with information that served as the health basis in 1973; background information on the chemical and environmental aspects of mercury, including the global cycling of mercury and the levels of mercury in media with which U.S. population groups come into contact (Chapter 3); mercury pharmacokinetics and metabolism, where factors of absorption, biotransformation, tissue distribution, and excretion of mercury are discussed with reference to the toxicity of the element (Chapter 4); mercury toxicology, discussing the various acute, subacute, and chronic health effects of mercury in man and animals (Chapter 5); and a human health risk assessment for mercury, where key information from the preceding chapters is presented in an interpretive and quantitative perspective highlighting those health effects of most concern for U.S. populations (Chapter 6).

This report is not intended to be an exhaustive review of all the mercury literature, but is focused upon those data thought to be most useful and relevant for human health risk assessment purposes. Particular emphasis is placed on delineation of health effects and risks associated with exposures to airborne mercury in view of the most immediate use intended for this present report, i.e., to serve as a basis for decision making regarding the possible reconsideration and revision of the 1973 emission standard. Health effects associated with the ingestion of mercury or with exposure via other routes are also presented; however, a comprehensive discussion of these effects is not within the purview of this report. The background information provided at the outset on sources, emissions, and ambient concentrations of mercury in various media is presented in order to provide a general perspective against which to view the health effects evaluations contained in later chapters of the report.

The Agency recognizes that the regulatory decision-making process is a continuous one; therefore, should new information become available in the future that would warrant a reevaluation of the information contained herein, the Agency will undertake such an evaluation as part of its mandate to protect the health of the general U.S. population.

2. SUMMARY AND CONCLUSIONS

This Chapter mainly summarizes the information contained within the text of this report. However, for comparative purposes, a brief synopsis is presented of the scientific information that served as the health basis in the promulgation of the 1973 National Emission Standard for Mercury.

2.1 THE NATIONAL EMISSION STANDARD OF 1973

On April 6, 1973, the U.S. Environmental Protection Agency promulgated a National Emission Standard for Mercury as a Hazardous Air Pollutant under Section 112 of the Clean Air Act (38 FR 8820). The scientific information which served as the health basis for the standard is presented below.

2.1.1 Direct Exposure Effects

By 1973, the fact that exposure to metallic mercury vapor caused central nervous system injury and renal damage was well established. Prolonged exposure to about 100 µg Hg/m^3 of mercury vapor involved a definite risk of mercury intoxication. To determine the ambient air level of mercury that did not impair health, the impact of airborne burden was considered in conjunction with water and food burdens. Methyl mercury compounds were considered to be the most hazardous form of mercury and the overall human body burden was believed to be mainly derived from the ingestion of methyl mercury in the diet, particularly via fish which concentrate this form of mercury through the food chain. At the time that the first standard was set, it was considered prudent to assume that exposures to methyl mercury (diet) and mercury vapor (air) were equivalent and additive.

Also known by 1973 was the fact that methyl mercury compounds, when ingested in sufficient amounts, could produce severe and irreversible damage to the central nervous system both in the adult and in the human fetus. The effects occurring at the lowest body burden were non-specific symptoms such as paresthesia. These first symptoms of intoxication had been observed in adults after prolonged intake of approximately 300 µg Hg as methyl mercury per 70 kg body weight. It was assumed that a safety factor of ten would provide satisfactory protection against genetic lesions and poisoning of the fetus and of children. Thus, it was determined that the total intake of methyl mercury should not exceed 30 µg Hg/day/70 kg body weight. Because the burdens of mercury vapor and methyl mercury were assumed to be equivalent and additive, it followed that the daily absorption of both forms of mercury should not exceed 30 µg Hg/70 kg body weight.

It was also determined from estimates of average diets that, over a considerable period of time, mercury intakes of 10 µg Hg/day/70 kg body weight might be expected. Thus, in order to restrict total intake to 30 µg Hg/day/70 kg body weight, the average mercury intake from air would have to be limited to 20 µg Hg/70 kg body weight. To maintain this level, the air would have to contain an average concentration of no more than 1 µg Hg/m^3, assuming inhalation of 20 m^3/day by the 70-kg adult.

2.1.2 Indirect Exposure Effects

Prior to promulgation of the standard, data on the environmental transport of mercury did not permit a clear assessment of the impact of atmospheric mercury emissions on aquatic and terrestrial environments. Consequently, the standard promulgated in 1973 was "intended to protect the public health from the effects of inhaled mercury," taking into consideration dietary contributions to total body burden, but it did not account for the effects of atmospheric mercury on other environments that, in turn, contribute to indirect exposures to mercury.

2.2 FINDINGS OF CURRENT REPORT

The findings of this report are based mainly on a review of the scientific literature published since the promulgation of the standard in 1973. However, literature published prior to 1973 has also been evaluated if it is still relevant to assessment of human health risks from airborne mercury. The following summary follows the format of the ensuing chapters.

2.2.1 Mercury Background Information

2.2.1.1 The Global Cycle--Despite intensive research in recent years, many details, both quantitative and qualitative, on the global cycling of mercury remain obscure. Elemental mercury vapor, Hg^0, emitted from land and water surfaces, is the principal species in the atmosphere and responsible for long distance (100 to 1,000 kilometers) transport of mercury. The residence time of this form of mercury is on the order of months, possibly years. A "soluble" form of mercury, of unknown chemical species, is also present in the atmosphere, but to a lesser extent. Soluble mercury is returned by precipitation to the earth's surface. Its residence time in the atmosphere is believed to be only on the order of days.

Widely varying estimates (from 10 to 80 percent) have been made for the anthropogenic contribution of mercury to the atmosphere. The figure arrived at in this report is approximately 25 percent. Anthropogenic input of mercury into bodies of fresh water is believed to have increased mercury levels in waters and sediments by factors two to four as compared to pre-man eras. Oceanic sediments are believed to be the ultimate depository of mercury in the form of insoluble mercuric sulfide. The amount of mercury in oceanic water is believed to be so large (on the order of tens of millions of tons) that man's impact has been negligible. However, anthropogenic mercury sources have had substantial impact on the levels of mercury in aquatic organisms in marine coastal waters near urban centers.

2.2.1.2 Biomethylation of Inorganic Mercury--Within the context of the global cycle, microbially-mediated methylation and demethylation reactions of mercury take place in the sediments of fresh and ocean waters. These processes also can take place within, and on, organic particulate microenvironments within the water column, especially in eutrophic and hypereutrophic aquatic systems. These reactions play a key role in the entry of methyl mercury into the human diet. Microorganisms are capable of methylating inorganic mercury via a non-enzymic reaction with methyl cobalamines. Many types of microorganisms are capable of methylating inorganic mercury. The most efficient and effective are certain aerobes and facultative anaerobes; less efficient are strict anaerobes such as methanogenic bacteria. Both mono- and dimethyl mercury compounds are formed, depending on pH and other conditions. Monomethyl mercury compounds rapidly diffuse from the microorganisms and rapidly accumulate in aquatic food chains. The highest concentrations are found in large predatory fish at the top of the aquatic food chain, e.g., trout, pike, and bass in fresh water; tuna, swordfish, and red snapper in oceanic water.

Many factors influence the extent of accumulation of methyl mercury in fish, including not only the species of fish, but also the age of the fish, the levels of mercury in sediment, the presence of zooplankton, organic content of sediments and particulates in the water column, water temperature, redox potential, and dissolved oxygen content. Current studies suggest that long-distance atmospheric transport and acidification of rain water are correlated with elevated levels of methyl mercury in fresh water fish.

Methyl mercury compounds are demethylated by microorganisms present in the environment. The accumulation of methyl mercury in the food chain ultimately depends upon an ecolcgical balance between methylation and demethylation reactions as well as trapping within organisms and chemical complexes.

2.2.1.3 Levels of Mercury in Air, Water and Food--Concentrations of mercury in the atmosphere have been estimated to be in the vicinity of 20 ng Hg/m^3. Most recent observations, as yet unconfirmed, indicate that a more accurate estimate of average atmospheric levels is in the range of 2-10 ng Hg/m^3. Concentrations of mercury in fresh water are around 25 ng Hg/l, most of which is probably in the mercuric (Hg^{++}) form. Concentrations of mercury in fish and fish products (the dominant food source of mercury in the human diet) average from 100 to 220 ng Hg/g fish, almost all (70 to 90 percent) of which is methyl mercury. Tuna is eaten by approximately two thirds of all fish consumers in the U.S. However, on an individual consumer basis, freshwater fish, e.g., pike, bass, and trout, have the highest consumption rate.

In terms of total mercury, the diet greatly exceeds other media, including air and water, as a source of human exposure and absorption of mercury.

2.2.2 Pharmacokinetics and Biotransformation of Mercury in Man and Animals

2.2.2.1 Vapor of Metallic Mercury--Since 1973, new information has become available on the pharmacokinetics of inhaled vapor in man and on the biotransformation of elemental mercury in animal tissues. Although a complete pharmacokinetic model is not yet established, some principal features have been identified.

Uptake of mercury vapor is through inhalation and, probably, skin absorption, although the extent of uptake through the latter route is still unknown. Approximately 80 percent of the amount inhaled is retained and rapidly transferred to the bloodstream, where it is distributed to all tissues in the body. Mercury readily crosses the blood-brain and placental barriers, but accumulates to the greatest extent in the kidney. It is mainly excreted in urine and feces; however, it is also excreted in sweat, saliva, and, to a small extent, expired air. Due to the rapid oxidation of absorbed mercury vapor to divalent mercury in mammalian tissues, it is likely that most of the mercury accumulated in the kidney and other tissues and excreted is in the divalent form.

The whole body half-time of mercury in man is approximately 50 to 70 days. A rapid component in blood has a half-time of about three days, and a slower component has a half-time of about 30 days. A rapid component in the brain has a half-time of about 21 days. There is evidence of a much slower component in brain with a half-time on the order of several years.

Dissolved elemental mercury, Hg^{o}, is believed to be the most important mobile species in mammalian tissues. It is oxidized to Hg^{++} by the hydrogen-peroxide-catalase complex in red blood cells, liver, kidney and, probably, many other tissues. Ethanol, at low non-intoxicating doses, can inhibit this oxidation process and, thereby, lead to a decreased retention of inhaled mercury. Inorganic divalent mercury, Hg^{++}, is reduced to Hg^{o} in liver and kidney tissues and, probably, in other tissues as well. The biochemical mechanism for this reduction has not yet been identified in mammalian cells but is well established in bacteria to the extent that even the genetics, sequence of the enzymes, and active site have been determined through DNA-sequence analysis.

There is evidence that inhaled mercury vapor can induce the metal-binding protein metallothionein in kidney tissue and that mercury-selenium complexes may be formed after chronic exposure.

2.2.2.2 Compounds of Inorganic Mercury--Since 1973, new information has been published on the kinetics of tracer doses of inorganic mercury in man. However, a complete pharmacokinetic model for either mercurous or mercuric forms of mercury has not yet been established.

Although it is known that mercurous chloride is slowly and incompletely absorbed after oral dosing, amounts sufficient to lead to symptoms of mercurialism can be absorbed on a chronic basis. Once absorbed, mercurous mercury is probably converted to the mercuric form. Mercuric mercury, ingested as such, has a less than 15 percent rate of absorption following oral dosing. However, inferences from animal studies suggest that absorption of mercuric mercury may be as high as 50 percent in children and infants.

Mercuric mercury is distributed via the bloodstream to all tissues in the body but penetrates the blood-brain and placental barriers to a much lesser extent (approximately ten times less) than mercury vapor. As is the case with mercury vapor, the kidney concentrates inorganic mercury to a much greater extent than other tissues, and excretion is mainly via urine and feces.

The average biological half-time of a tracer dose of divalent inorganic mercury compounds in man is 42 days for the whole body and 26 days for blood.

2.2.2.3 Methyl Mercury Compounds--New information on the kinetics of methyl mercury in man and on the mechanisms of biotransformation and excretion does not change the picture that existed when the 1973 standard was promulgated. The pharmacokinetic model of methyl mercury in man is much further advanced than models for other forms of mercury.

Oral doses of methyl mercury are almost completely absorbed (approximately 95 percent). Methyl mercury is distributed in blood to all tissues of the body within a few days. Like other forms of mercury, methyl mercury readily crosses the blood-brain and placental barriers; however, unlike other forms, tissue concentrations of methyl mercury are much more uniform, with the kidney having somewhat higher concentrations than other tissues. The red blood cell-to-plasma concentration ratio is typically 20:1, the blood-to-brain ratio is approximately 1:5, and the blood-to-hair (newly formed) ratio is 1:250.

Approximately 80 percent of total methyl mercury excretion is via the feces. Methyl mercury is also secreted in bile and reabsorbed back into the bloodstream to form an enterohepatic cycle. The remainder undergoes demethylation by flora in the intestine and is excreted as inorganic mercury. Experimental studies indicate that a functioning enterohepatic cycle and active gut flora are essential to the excretion of mercury after doses of methyl mercury. It is known that suckling animals cannot excrete methyl mercury in bile and, therefore, are unable to excrete significant amounts of methyl mercury from the body. The implication of these animal data to humans is unknown and no information is available on human infants.

The average biological half-time of methyl mercury in human adults is approximately 70 days in the whole body and 50 days in the blood compartment. The biological half-time in brain is probably similar to that of the whole body or slightly longer. A wide range of biological half-times (up to 120 days in the whole body) has been reported in adults substantially exposed to methyl mercury. The reason for this wide range is unknown, but in experimental studies, the type of diet was shown to affect half-times in the experimental animals.

2.2.3 Toxic Effects of Mercury in Man and Animals

The following section summarizes the toxic effects of mercury in man and animals, with emphasis placed on effects arising from long-term low-level exposures. Where possible, greater attention has been focused on direct observations on human subjects.

2.2.3.1 Vapor of Metallic Mercury--Since 1973, a number of clinical and epidemiological studies have been published on workers occupationally exposed to mercury vapor. In general, the findings of these studies support the earlier findings that existed when the mercury standard was promulgated.

Occupational studies have shown that chronic exposure to mercury vapor affects primarily the central nervous system and the kidneys. Effects associated with the lowest exposure levels--below 100 µg Hg/m^3--produce non-specific symptoms such as introversion, insomnia, and anxiety. Biochemical alterations have been observed in enzymes of plasma and red blood cells, and increases in urinary excretion of specific proteins and enzymes are known to occur. Higher chronic exposures produce more pronounced effects in cognitive function, such as short-term memory loss and changes in personality traits (e.g., increased anxiety and introversion). An overall body tremor, typical to mercurialism cases, signals the motor disfunctioning of the central nervous system. No threshold for these and other effects has been clearly established, although effects have not been seen at air concentrations around 10 µg Hg/m^3

Renal effects may be mediated through an autoimmune mechanism and may exhibit wide individual ranges of sensitivity. Experimental studies on this sensitivity indicate the possibility of a genetic component related to the major histocompatibility complex.

Effects on both the nervous system and kidney are usually reversible, particularly if the effects are mild. Studies have shown that motor effects reverse more readily than cognitive and neurotic effects.

Information is generally lacking on reproductive and developmental effects of inhaled mercury vapor.

2.2.3.2 Inorganic Compounds of Mercury--Virtually no new information on the effects of inorganic compounds of mercury on humans has become available since 1973. In case studies on two adults, it was shown that many years of chronic oral intake of mercurous chloride (250 mg/day) resulted in typical signs of mercurialism and chronic renal failure. Chronic oral exposure to mercurous chloride has also caused acrodynia or Pink's disease in children. Great differences in individual sensitivity have been reported for such effects, although, generally, acrodynia associated with urinary levels of 50 µg Hg/l is reversible in children. Based upon comparison studies to mercury vapor and mercurous salts, it is assumed that chronic exposure to compounds of mercuric mercury would mainly affect kidney function. Experimental studies supporting the above evidence are lacking.

2.2.3.3 Compounds of Methyl Mercury--Since 1973, new information has become available on a population exposed to dietary methyl mercury. Findings from the study population generally support the evidence that existed in 1973 and confirm the special sensitivity of prenatal life to methyl mercury exposure. Milder effects at dose levels lower than those observed in 1973 have been reported for the first time in prenatally exposed infants. The possibility has been raised of delayed effects appearing in adults several years after the cessation of exposure.

Methyl mercury primarily damages the central nervous system in both adults and prenatal infants. Prenatal exposures at the lowest recorded levels produce signs of psychomotor retardation in infants. Recent studies indicate that male infants may be more sensitive than females at these low levels of maternal dietary intake. Substantially higher prenatal exposures, some only occurring in the last trimester of pregnancy, produce a severe form of cerebral palsy. Although detailed mechanisms of methyl mercury poisoning are not known, prenatal effects appear to be due to a derangement of the normal processes of growth and development of the central nervous system. Ongoing studies indicate (based on estimated blood levels in the mother during pregnancy) that the fetus is about three times more sensitive than the adult to methyl mercury exposures.

Effects on the adult central nervous system result from focal damage to specific areas of the brain, principally the cortex of the cerebellum and the visual cortex. The first symptoms of methyl mercury poisoning in adults are non-specific, e.g., paresthesias and malaise. These effects are believed to have a low frequency of occurrence (approximately 5 percent) in the general population and are seen at blood levels ranging from 200 to 500 ng Hg/ml, which correspond to chronic oral daily intakes of approximately 3 to 7 μg Hg/kg body weight. Evidence is conflicting on the degree of reversibility of these first symptoms of poisoning. Dietary intake levels of methyl mercury that produce irreversible destruction of neurons in the cerebellar and visual cortices leading to permanent signs of ataxia and constriction of the visual field are probably at least twice as high as those levels causing mild symptoms.

2.2.4 Human Health Risk Assessment of Mercury in Air

2.2.4.1 Direct Exposure Effects--Because the 1973 standard was based on the direct exposure effects from airborne mercury, taking into consideration the contribution of dietary mercury intake to total body burden, a similar approach has been taken here to determine to what extent new information has changed the perspective on direct risks from mercury in air.

A new evaluation confirms that, while mercury vapor still accounts for the major fraction of airborne mercury, particulate forms of mercury do exist in the atmosphere. The diet is by far the dominant, if not the sole source of human exposure to methyl mercury compounds. In addition, a current evaluation indicates that the diet is also the dominant source of compounds of inorganic mercury. In comparing different routes of exposure, contribution of airborne mercury is between one-tenth and one-twentieth of the total daily amount of mercury absorbed into the body.

An analysis of dose-response and dose-effect relationships indicates that current levels of mercury in the atmosphere, irrespective of chemical species, would present a negligible risk of adverse health effects from direct airborne exposures. Current atmospheric levels are believed to be 20 ng Hg/m^3 or less. Effects of mercury vapor on human health have not been detected below 1 μg Hg/m^3, and serious debilitating effects have not been observed in occupational settings where workers have been exposed for periods of months to years to air concentrations below 100 μg Hg/m^3. Even assuming that all the mercury in the atmosphere were in the form of methyl mercury compounds, it would require an atmospheric concentration of 10 μg/m^3 to produce an inhalation intake equivalent to an oral intake of 200 μg/day (believed to be the approximate lowest observed effect level for adults). Even taking into account the greater sensitivity of the fetus, there has not been an appreciable change in the health basis upon which the 1973 standard was based.

2.2.4.2 Indirect Exposure Effects--Mercury in the atmosphere has the potential to produce indirect exposure effects through increasing levels of methyl mercury in edible tissues of freshwater fish. As previously noted (see Section 2.1.2), the effect of atmospheric mercury on indirect exposures was not considered in the 1973 promulgation because of insufficient information on the environmental fate of airborne mercury.

While current knowledge of the fate of airborne mercury is still incomplete, studies in the last ten years strongly suggest the possibility of long-distance transport of mercury from sources of pollution to deposition of soluble mercury on land and water. Runoff from land further transfers mercury to bodies of fresh water. While it was known in the past that local pollution of lakes and rivers could give rise to unacceptably high concentrations of methyl mercury in fish that exceed Federal guidelines, an important recent finding is that high levels of methyl mercury are also found in certain lakes remote from anthropogenic sources. In addition, the problem of long-distance transport is exacerbated by the acidification of rainwater in certain areas of the United States. A statistical correlation has been found between the acidity of lakes and elevated levels of methyl mercury in fish.

Many possible mechanisms for this elevation may exist, but the overall effect is that methyl mercury levels in fish are, to some extent, indirectly affected by airborne mercury and acid deposition. The question, therefore, arises as to what extent changes in current atmospheric levels would affect levels of methyl mercury in edible freshwater fish, and what would be the predicted impact on human health.

Although the answer to the first question cannot be definitively quantified at this time, it could be conjectured that if airborne mercury levels increased from current levels of 5 to 20 ng Hg/m^3 to the 1,000 ng Hg/m^3 level that was used as a guideline in setting emission limits for source categories regulated by the current standard, the environmental consequences could be severe. At some point in this sharp rise in atmospheric air concentrations, levels in fish would increase to unacceptably high values.

The health impact on the U.S. is also difficult to express in quantitative terms. Both action guidelines by the Food and Drug Administration and state regulations already exist that effectively stop consumption of fish if methyl mercury levels exceed 1 µg Hg/g wet weight. The outcome, therefore, would probably be the same as in Scandinavian countries, where elevated mercury concentrations in edible tissue of fish have resulted in the banning of fish for consumption purposes from a large number of freshwater lakes. Local communities, such as reservations of native American populations dependent on freshwater fish as a main food item, may suffer health consequences if federal and local regulations do not prevent the consumption of contaminated fish in these communities.

In conclusion, a more comprehensive reevaluation of existing information would be required if the potential for indirect exposure effects were considered.

3. MERCURY BACKGROUND INFORMATION

3.1 PHYSIOCHEMICAL PROPERTIES OF MERCURY

Mercury is unique amongst the metals as being the only metal in a liquid form at room temperature. The metal has a melting point of -38.9°C and a boiling point of approximately 356°C. The atomic weight is 200.59. At 20°C the specific gravity of the metal is 13.546 and the vapor pressure is 0.0012 mm of mercury. This high vapor pressure of the liquid metal is of significance with regard to human exposures to the vapor. A saturated atmosphere at room temperature contains mercury vapor at a concentration of approximately 20 mg/m^3. This concentration of the metal is over two orders of magnitude greater than the currently accepted maximum allowable concentration for occupational exposure.

Mercury exists in a wide variety of physical and chemical forms. It has three oxidation states: Hg^o (metallic), Hg_2^{++} (mercurous) and Hg^{++} (mercuric mercury). It forms stable organometallic compounds with alkyl, e.g. CH_3Hg^+ and CH_3HgCH_3 (monomethyl and dimethyl mercury) and aryl, e.g. $C_6H_5Hg^+$ (phenyl mercury) groups. This review chapter will discuss only those chemical and physical forms of mercury that are involved in the biogeochemical cycle and the forms to which humans are principally exposed in the environment.

3.1.1 Sampling and Analysis

Mercury and its compounds in the environment have always presented sampling and analytical challenges not encountered with most environmental pollutants. Unlike most metals, mercury in the atmosphere is usually found as elemental mercury vapor. However, mercury compounds can also be present as part of the particulate matter; thus, making certain vapor-sensing analytical methods unsatisfactory. In addition, there is reason to be concerned with the valence state of inorganic mercury compounds and the presence, in some instances, of both aryl and alkyl organic compounds. The analytical problems related to the estimation of mercury in air are further compounded when mercury determinations must be made in biota or biospecimens such as blood, urine, and tissue. In such samples, elemental mercury is rarely determined as such, but it may become necessary to differentiate between inorganic and organic forms. Henderson et al. (1974) have shown that there are at least 3 different forms of mercury which are identifiable in urine specimens from workers exposed to mercury.

Historically, all of these problems have been compounded by the considerable analytical challenge of determining sub-microgram quantities of mercury in the presence of other air contaminants or the large amount of organic matter and other substances accompanying mercury in all biological specimens. For many years, levels of mercury vapor present in the workplace have been determinable by sensitive and almost mercury-specific devices, notably the ultraviolet mercury vapor meters, which are in fact portable atomic absorption units. Their use in general was limited to the determination of workplace levels of mercury vapor, and in all probability even early studies of mercury vapor exposure levels were of relatively good quality insofar as the accuracy and specificity of the measurements were concerned. Most such studies, of course, did not attempt to define the non-vapor exposures, and some could have been influenced by certain organic vapors which interfere with the performance of mercury vapor detectors.

Until the 1960's, most biospecimen analyses were difficult to perform and required lengthy acid digestions under reflux conditions in order to convert the mercury to mercuric ions making it amenable to a dithizone colorimetric procedure. The difficulties and uncertainties inherent in these procedures were of such magnitude that they tended to discourage analyses, particularly in the case of blood samples where very small quantities of mercury had to be released from large amounts of blood constituents. It is probable that for this reason, until the advent of other methods, urinary mercury analyses, though tedious, were performed in preference to blood mercury analyses. It is also noteworthy that analytical studies performed prior to the development of modern techniques should be considered with an awareness that the analytical results may have been subject to errors of which the investigators were unaware. A comprehensive review (up to 1972) of all of the sampling and analytical methods for mercury in air and biospecimens was published by Smith (1972).

The introduction of the "cold vapor" methods of analysis in the 1960's marked the beginning of a new era in mercury analysis, and in general, this method and its many subsequent modifications as well as several other methods have completely revolutionized the analysis of any kind of sample for mercury content. When applied to biological specimens of any kind, the basic approach of all such cold vapor methods is to convert the mercury in a small sample to mercuric ion, then reduce it to elemental mercury with a reductant such as stannous chloride and measure the mercury vapor in a modified atomic absorption spectrophotometer. A number of recent publications have utilized this general technique for air, biological and environmental samples (Hatch and Ott, 1968; Gage and Warren, 1970; Smith, 1972; Henderson et al., 1974; Rathje and Marcero, 1976; Bourcier et al., 1982). A popular alternative to the cold vapor technique utilizing conventional flame atomic absorption is the flameless method which ordinarily utilizes a graphite furnace. Methods based on this approach are widely used for all types of samples and generally achieve very much lower detection limits (Lindstedt, 1970; Kubasik et al., 1972; Trujillo and Campbell, 1975; McCullen and Michaud, 1978; Menke and Wallis, 1980; Diggs and Ledbetter, 1983). Once any method has succeeded in releasing mercury vapor, certain other detection techniques become feasible, and one such method in current use relies upon the amalgamation of a thin gold layer deposited on a quartz crystal with measurement based on the piezoelectric effect (Scheide and Taylor, 1974; 1975).

With respect to the measurement of levels of mercury vapor in air, it is presently possible to make measurements in the workplace using improved direct-reading mercury vapor meters, direct-reading colorimetric indicator tubes, or passive badge monitors (McCammon and Woodfin, 1977); or samples may be collected on an adsorbent material such as charcoal (Yrjänheikki, 1978), Hopcalite (McCullen and Michaud, 1978; Menke and Wallis, 1980), or silver wool (Bell et al., 1973a; Long et al., 1973). Whenever particulate mercury compounds must be collected, such methods must be preceded by conventional particulate matter collection procedures which ordinarily rely on filtration using high efficiency filters (Trujillo and Campbell, 1975; Menke and Wallis, 1980).

In workplace environments, mercury may be present at concentrations ranging from several micrograms to more than 100 micrograms per cubic meter, whereas in the uncontaminated general atmosphere, background levels are measured in nanograms per cubic meter, and even contaminated atmospheres will be found to contain but a few micrograms per cubic meter. Direct reading devices and certain other methods of sampling and analysis suitable for workplace measurements, therefore, are generally not sufficiently sensitive to detect background environmental levels. Hence, methods must be selected which either remove the mercury from a relatively large volume of air, or which are specifically designed to be extremely sensitive (Bell et al., 1973a; Long et al., 1973; Scheide and Taylor, 1974; USEPA 40 CFR 61, 1981).

A number of sampling and analytical techniques are satisfactory for workplace air samples (Krause et al., 1971; Moffitt and Kupel, 1971; Rathje et al., 1974; Trujillo and Campbell, 1975; McCammon and Woodfin, 1977; McCullen and Michaud, 1978; Yrjänheikki, 1978; Diggs and Ledbetter, 1983), and although some of these may be applied to analyses of the general environment, they frequently lack required sensitivity.

Most methods for the analysis of blood, urine, and other biological specimens rely on the same analytical methods applicable to air samples, but require some sort of pretreatment to liberate the bound mercury. Several published methods may be used for virtually any type of biological samples (Gage and Warren, 1970; Moffitt and Kupel, 1971; Henderson et al., 1974), urine specimens (Rathje, 1969; Krause et al., 1971; Kubasik et al., 1972; Henderson et al., 1974; Stopford et al., 1978; Bourcier et al., 1982), or blood (Krause et al., 1971; Kubasik et al., 1972; Stopford et al., 1978; Bourcier et al., 1982).

Organic forms of mercury, which are less frequently analyzed, generally require more sophisticated analytical approaches based on gas-liquid chromatography, GC-mass spectroscopy, or methods which preferentially separate organic compounds from ionic species and which thereafter may be analyzed for mercury content by conventional means (Gage and Warren, 1970; Hoover et al., 1973; Henderson et al., 1974; Trujillo and Campbell, 1975).

The collection and analysis of workplace samples is believed to be influenced in a somewhat unusual manner by the microenvironment which may be created by workers' clothing or contaminated skin (Bell et al., 1973a; Stopford et al., 1978). It has been argued that by using typical personal sampling devices, an environment enriched in mercury vis-a-vis mercury-contaminated clothing is actually measured. Although this measurement may in fact more accurately reflect a worker's exposure, there is concern that past studies on which current standards were based were made using area measurements which were not influenced by this microenvironment; hence, false conclusions concerning the effects of the measured values could be inferred. Obviously the air-urine mercury level relationships established in the past could likewise be affected by this phenomenon. Other problems which have been identified in the unique environment of a mercury cell room in which chlorine is manufactured arise from the simultaneous presence of elemental chlorine and mercury which may combine to produce chlorides not detected by vapor-sensing devices (Menke and Wallis, 1980).

In summary, sampling and analytical methods are presently available which make it possible to perform estimations of mercury and its compounds at extremely low levels in air, or virtually any matrix of interest with respect to contamination of the environment. Such analyses may be performed rapidly on very small samples and with a high degree of accuracy or precision. Many important studies of the past (prior to the 1960's) were hampered by the absence of such methodologies, and findings of these studies should always be judged with an awareness of the shortcomings inherent in the mercury analyses.

3.2 ENVIRONMENTAL CYCLING OF MERCURY

3.2.1 Global Cycles

The global cycle of mercury has recently been reviewed by Nriagu (1979), the National Academy of Sciences (1978), and Jernelov et al. (1983). The global cycle of mercury involves degassing of the element from the earth's crust and evaporation from natural bodies of water, atmospheric transport believed to be mainly in the form of mercury vapor, and deposition of mercury back onto land and water. Mercury ultimately finds its way to sediments in water, where, particularly in oceanic sediments, the turnover is very slow.

Andren and Nriagu (1979) have indicated that the residence time of mercury in the atmosphere may vary from approximately 6 to 90 days. A more recent estimate of total mercury in the atmosphere indicates a turnover time of 0.3 - 2 years. An as yet unidentified soluble form of mercury, accounting for a small fraction of total mercury, is estimated to have a turnover time of about a few weeks (Jernelov et al., 1983). Residence times of mercury are on the order of 1000 years for soils, 2000 years for oceans, and are measured in millions of years for sediments.

The measurement of mercury in extremely low environmental concentrations is frequently close to the limit of detection of many current methods. With this in mind, estimates of quantities of mercury entering the environment from both natural and anthropogenic sources are presented in Table 3-1.

The predominant reservoir for mercury is ocean water, containing on the order of 40 million metric tons (Nriagu, 1979). Estimates of the yearly amounts of mercury finding its way to the ocean indicate that atmospheric deposition accounts for the major amount, approximately 11,000 metric tons per year, with land runoff accounting for about 5,000 metric tons per year.

TABLE 3-1. SOURCES OF MERCURY IN THE ENVIRONMENT (1971)

Source	Amount Metric tons/year
Natural	
degassing of earth's crust	~30,000
Anthropogenic	
worldwide mining	10,000
combustion of coal	3,000
combustion of oil	400-1,500
smelting of metal sulfide ores	1,500
steel cement phosphates	500

Source: Nriagu, 1979; World Health Organization, 1976.

Little is known about localized high concentrations of mercury in oceanic waters. Undersea volcanos and mercury-rich ores on the ocean bed may be responsible for high local or regional levels (for review, see Dahlem Conference, 1983). The elevation of mercury concentrations in ocean surface waters from anthropogenic sources is a possibility since surface waters mix very slowly with the deep waters of the ocean.

In comparison to ocean water, the reservoir for mercury in fresh water is considerably less, averaging a few thousand metric tons with an additional several hundred tons contained in freshwater biota (National Academy of Sciences, 1978).

Recently, the pattern of mercury emissions to bodies of fresh water has been changing. Due to the imposition of mandatory controls, industrial release of mercury from point sources, such as chlor-alkali plants, has diminished considerably, thus, resulting in reductions of mercury emissions to such freshwater bodies. However, in the case of chlor-alkali plants, the release of mercury to the environment is small in comparison with, for example, fossil-fueled power plants; hence, the elimination of mercury discharge from chlor-alkali plants has had more of a local effect than an overall global effect (Wallin, 1976).

On a global scale, it has recently become apparent that long-distance atmospheric transport of mercury and acidification of rainwater have become increasingly important factors in the dissipation of mercury to freshwater bodies.

The atmosphere serves as the smallest reservoir for mercury in the environment, containing only about a thousand metric tons of mercury (National Academy of Sciences, 1978). Mercury entering the atmosphere from degassing of the surface of the earth varies widely, but a commonly quoted figure is 30,000 metric tons per year. Wide estimates have been made of the proportion of mercury in the atmosphere due to anthropogenic sources, with figures varying from 10 to 80 percent. In comparisons to pre-man emissions of mercury to the atmosphere, Jernelov and co-workers (1983) believe that the present atmospheric emissions represent at least 20 percent of the total emissions.

As noted above, because the atmosphere and fresh water contain much less mercury, the impact of man-made release of mercury would be expected to be much greater on these smaller reservoirs, especially in instances where the release is direct. For example, it is estimated that the mercury content of lakes and rivers may be increased by a factor of 2 to 4 due to man-made release (National Academy of Sciences, 1978). In contrast, it is estimated that oceanic concentrations have not appreciably changed in recent history.

3.2.2 Chemical and Biochemical Cycles of Mercury

This overall global cycle of mercury is the result of extremely complex physical, chemical, and biochemical processes occurring in the main reservoirs and interfaces between these reservoirs. Most of these processes are poorly understood but, nevertheless, certain very important fundamental discoveries have been made in recent years and these are summarized below. It should be recognized that this is an incomplete picture and that this area is undergoing very active research at the present time.

The most important single discovery in understanding the chemical and biochemical cycles of mercury in the environment was made by Swedish investigators in the 1960s (for a review, see National Academy of Sciences, 1978). An intensive investigation into the source of methyl mercury compounds in freshwater fish led to the finding that microbial activity in aquatic sediments can result in the methylation of inorganic mercury in the environment (Jensen and Jernelov, 1967).

The methylation of ionic mercury in the environment appears to occur under a variety of conditions: in both aerobic and anaerobic waters, in sediments, in the presence of various types of microbial populations (both anaerobes and aerobes), and in different types of freshwater bodies such as eutrophic and oligotrophic lakes.

The presence of methyl mercury in many species of ocean fish, including wide-ranging species such as tuna and shark, strongly suggests that the methylation process can occur in oceans as well as in bodies of fresh water.

The mechanism of synthesis of methyl mercury compounds from inorganic precursors is now well understood in both the terrestrial environment and in the sea (Wood and Wang, 1983). The most probable mechanism for methylation of inorganic mercury involves the non-enzymic methylation of mercuric mercury ions by methyl cobalamine compounds (Vitamin B_{12}) that are produced as a result of bacterial synthesis. However, other pathways both enzymic and non-enzymic may play a role (Beijer and Jernelov, 1979).

To date, two different mechanisms have been determined for methyl-transfer from methyl-B_{12} to heavy metals: (1) electrophilic attack by the attacking metals on the Co-C bond of methyl-B_{12} and (2) methyl-radical transfer to an ion-pair between the attacking metal ion and the corrin-macrocycle.

The ecological significance of B_{12}-dependent biomethylation is best illustrated by B_{12}-dependent and B_{12}-independent strains of Clostridium cochlearium. The B_{12}-dependent strain is capable of methylating Hg^{II} salts to CH_3Hg^{II}, whereas the B_{12}-independent strain is incapable of catalyzing this reaction. Both strains transport Hg^{II} into cells at the same rate, but the B_{12}-independent strain is inhibited by at least a 40-fold lower concentration of Hg^{II} than the B_{12}-dependent strain. The result demonstrates that Clostridium cochlearium uses biomethylation as a mechanism for detoxification, giving the organism a clear advantage in mercury-contaminated systems. This biomethylation capability has been shown to be plasmid-mediated (Pan Hou and Imura, 1982).

Once methyl mercury is released from the microbial system, it enters food chains as a consequence of its rapid diffusion rate. In the estuarine environment, the reduction of sulfate by Desulfovibrio species to produce hydrogen sulfide is quite important in reducing CH_3Hg^+ concentrations by $S^=$-catalyzed disproportionation to volatile $(CH_3)_2Hg$ and insoluble HgS. There is evidence to support the notion that membrane transport of methyl mercury is diffusion controlled. Fluorescence techniques and high resolution nuclear magnetic resonance (NMR) show that diffusion is the key to CH_3Hg^+ uptake (Wood et al., 1978; Lakowicz and Anderson, 1980). Also, a field study of the uptake of CH_3Hg^+ by tuna fish in the Mediterranean fits the diffusion model for biota in tuna food chains (Buffoni and Bernhard, 1982).

Microorganisms have been isolated which catalyze the reactions described above for both the forward reaction to Hg^0 and the back reaction to CH_3Hg^+ as presented below:

$$CH_3Hg^+ \rightleftarrows Hg^{2+} \rightleftarrows Hg^0$$

The enzymes which carry out the forward reactions are coded by DNA on bacterial plasmids and transposons and not by normal chromosomal genes (Silver, 1984). Therefore it is not too surprising that mercuric and organomercurial strains of bacteria have been isolated from a variety of ecosystems such as soil, water, and marine sediments (Friello and Chakrabarty, 1980; Olson et al., 1979, 1981; Timoney et al., 1978; Vonk and Sijpesteijn, 1973). The enzymology of methyl mercury hydrolysis and mercuric ion reduction is now understood in some detail (Silver, 1984). In fact, the sequence of the active site of mercuric ion reductase is now determined and has been found to be identical to that of glutathione reductase (Williams et al. 1982; Friello and Chakrabarty, 1980). Clearly, the reduction of Hg^{2+} to Hg^0, which is volatile, represents a very effective detoxification mechanism. Much less is known about the reverse reaction, that is, the oxidation of Hg^0 to Hg^{2+}. However, an enzyme which is critical to the oxygen cycle (catalase) will carry out this reaction. Microbial methylation of mercuric ion is also widespread (Vonk and Sijpesteijn, 1973; Hamdy and Noyes, 1975). Biomethylation has been shown to occur in sediments and in human feces. The important role played by sulfide in the biological cycle for mercury is presented in the equation below:

$$2\ CH_3Hg^+ + H_2S \rightarrow (CH_3)_2Hg + HgS$$

Hydrogen sulfide is very effective at volatilization and precipitation of mercury through disproportionation chemistry in the aqueous environment. Such reactions occur only in polluted lakes, rivers, coastal zones, estuaries, and salt marshes where _Desulfovibrio_ species have access to sulfate in anaerobic ecosystems.

Once in the atmosphere, volatile organometals, such as dimethylmercury, are unstable since metal-carbon bonds are susceptible to homolytic cleavage by light.

Brosset (1981a) has studied the circulation of mercury in air and natural waters with an emphasis on understanding the mechanisms of the long-distance transport and deposition of this element. Mercury is present in the atmosphere, not only as the water-insoluble mercury vapor, but also in water-soluble forms as well. The origin and chemical nature of these water-soluble forms is not well understood, but it is known that they are present in particulate matter in the atmosphere and do not occur as vapors.

The water-soluble forms of mercury may enter droplets of precipitation and be carried down to bodies of both fresh and marine water. On entering the water phase, the soluble forms of mercury are subject to reduction processes either chemical, depending on the local redox potential, or microbiological. The end product is metallic elemental mercury which, being highly diffusible, tends to diffuse back into the atmosphere. The remaining soluble mercury persists in the water phase for a sufficient period of time to attach to sediments and eventually forms the highly insoluble mercuric sulfide.

There also exists the possibility that atmospheric mercury in the particulate form may be deposited by dry deposition processes from the atmosphere into the water system following essentially the same chemical reaction as that for the wet deposition of these compounds. Mercury vapor may also be adsorbed to the terrestrial surface or absorbed into water.

The extent to which mercury may be taken up and reemitted from water or land surfaces to the atmosphere is still not understood in quantitative terms. Nevertheless, the general picture that emerges is one in which long-distance transport of mercury in the vapor phase is possible. Its uptake into water and reemission probably occur extensively, and the chemical conversion of mercury from the elemental to the ionic and to the organic forms is much more extensive than was originally believed.

Once methyl mercury enters the water phase as a soluble compound, it is rapidly accumulated by most aquatic biota and attains highest concentrations in the tissues of such large carnivorous fish as the pike in fresh water and the shark, swordfish, and tuna in marine water (Buffoni and Bernhard, 1982). Indeed, it is generally believed that the major amount of methyl mercury compounds in bodies of water are contained in the biomass of the system. The bioconcentration factors --the ratio of the concentration of methyl mercury in fish tissue to concentrations in water -- can be extremely large, usually on the order of 10,000 to 100,000 (U.S. Environmental Protection Agency, 1980).

The concentration of methyl mercury in fish tissue is of special interest in terms of human exposure to this form of mercury. The aquatic food chain is the main, if not the sole source of human exposure to methyl mercury, barring episodes of accidental discharge or misuse of man-made methyl mercury compounds. Thus, factors that affect concentrations of methyl mercury in edible fish tissue are of considerable importance in assessing potential human health risks from this form of mercury.

The uptake of mercury by plants has not been extensively studied. Uptake of mercury through apple tree roots to foliage was not detected for trees exposed to phenylmercury acetate (Ross and Stewart, 1962). Turf grass exposed to a $HgCl_2$-Hg_2Cl_2 mixture added in the root zone did not accumulate mercury (Gilmour and Miller, 1973). However, Browne and Fang (1978) observed direct uptake of mercury vapor by wheat leaves. Previously, Ratsek (1933) had noted direct uptake of mercury vapor by rose leaves. In the proximity of the Almaden mercury mines in Spain, Lindberg et al. (1979) noted that alfalfa plants accumulated mercury by a dual mechanism. The roots accumulated mercury according to the soil levels while the aerial plant material absorbed mercury directly from the atmosphere. It seems unlikely, however, that accumulation of mercury into plants is an important source of human exposure except possibly under special circumstances of local contamination and local consumption of the contaminated plants.

3.3 LEVELS OF MERCURY IN VARIOUS MEDIA

The industrial use of mercury and the release of mercury to the environment by the non-mercury industries (fossil fuel) has resulted in a general increase of mercury in the environment throughout the industrial revolution. This increase is well illustrated in a Swedish study conducted in the late 1960's (for details, see Swedish Expert Group, 1971).

The levels of mercury in air, water, and food have recently been summarized and reviewed by the World Health Organization (1976) and by the United States Environmental Protection Agency (1980). Most of the material presented in this section will be drawn from these two reviews with some additional, more recent information from specific papers as deemed appropriate.

3.3.1 Mercury in Ambient Air

Earlier reviews on mercury in the ambient air (World Health Organization, 1976; U.S. Environmental Protection Agency, 1980) suggested that the average concentration in the ambient atmosphere throughout the world appeared to be about 20 ng Hg/m^3. However, Jernelov et al. (1983), reviewing papers published since 1979, have concluded that background levels of about 2 ng Hg/m^3 as gaseous mercury exist in the lower troposphere of the Northern Hemisphere and 1 ng Hg/m^3 exists in the Southern Hemisphere. In regionally polluted areas, such as rural parts of Southern Sweden and Italy, concentrations more often lie between 3 to 4 ng Hg/m^3. In urban air, the average concentrations may be as high as 10 ng Hg/m^3. Industrialized areas may be even higher. In the plume of a coal-fired power plant, Lindberg (1980) reported concentrations of gaseous mercury in excess of 1000 ng Hg/m^3 within a few kilometers of the source. Isolated "hot spots" may have unusually high concentrations of mercury. For example, air levels up to 10,000 ng/m^3 have been found near rice fields where mercury fungicides have been used and mercury concentrations in the vicinity of mercury mines have been reported to be as high as 15,000 ng/m^3 (World Health Organization, 1976).

It is generally accepted that the predominant form of mercury in the atmosphere is mercury vapor present as a monatomic gas (World Health Organization, 1976). However, as indicated previously, other forms of mercury are also present. Johnson and Braman (1974), in a suburban site in Florida, found that approximately 60 percent of the mercury in the atmosphere was in the form of the vapor, but they also noted that 19 percent was present as inorganic ionic mercury and approximately 17 percent was present as methyl mercury compounds. There is general agreement that mercury in the particulate form accounts for only a very small fraction, on the order of about 4 percent, of the total mercury in the atmosphere. It should be noted at this point that the data of Johnson and Braman are specific to the Tampa Bay area and should only be applied to other circumstances with caution until corroborating data are obtained.

Brosset, referred to previously, has also found the presence of "soluble" forms of mercury in the atmosphere which may be both ionic and monomethyl mercury compounds (Brosset, 1981b).

The average daily absorption of atmospheric mercury in man has been quoted by the U.S. Environmental Protection Agency (1980) to be approximately

320 ng/70 kg body weight. This is based on assumptions that the average atmospheric concentration is 20 ng/m^3, that the adult male has a ventilation rate of 20 m^3, and that 80 percent of the inhaled rate is absorbed. Clearly, these figures require revision if the conclusions of Jernelov et al. (1983) are valid. Individuals living in nonpolluted rural areas would absorb approximately 16 ng Hg/70 kg body weight based on an air concentration of 1 ng Hg/m^3 and individuals in urban areas would absorb about 10 times this amount. It seems unlikely that atmospheric concentrations would exceed average values of 50 ng Hg/m^3 which would correspond to a daily intake of 800 ng Hg.

3.3.2 Mercury in Ocean and Coastal Waters

Levels of mercury in ocean water are generally well below 100 ng/l. Fitzgerald (1979) noted that the median value for oceanic water was approximately 59 ng/l. Recent estimates made by Matsunaga et al. (1979) indicate that the "reliable value for baseline mercury in nonpolluted waters is approximately 5-6 ng/l." The most recent review of the literature (Jernelov et al., 1983) concluded that average concentrations in the open ocean are about 3 ng Hg/l. Concentrations in coastal waters are somewhat higher, usually within the range of 5 - 10 ng Hg/l. The high concentration of chloride ion would suggest that at least the inorganic ionic form of mercury would form a complex with chloride. Measurements have been made on mercury speciation in seawater by Sillen and Martell (1971) that confirm that the principal species in seawater are chloride complexes of inorganic mercury.

3.3.3 Mercury in Drinking Water

A World Health Organization group (1976) concluded that levels of mercury in noncontaminated fresh water were usually less than 200 ng/l. Rainwater also appears to have concentrations generally below 200 ng/l, with most values ranging between 5 and 100 ng Hg/l. More recent reviews have indicated that noncontaminated mercury freshwater levels are much lower than 200 ng/l. Thus, in a review by Fitzgerald (1979), an average level of 25 ng/l was reported, and Jernelov et al. (1983) concluded that background concentrations are usually between 10 to 50 ng Hg/l.

The chemical form of mercury in fresh water and drinking water has not yet been well established, mainly because of difficulties of analysis. On theoretical grounds, one would expect mercury present mainly as Hg^{++} compounds in oxygenated water. Generally speaking, methyl mercury has not been detected in samples of fresh water. A review by McLean (1980) indicated that methyl mercury is present at concentrations close to the detection limit of currently used methods. More recently, Kudo et al. (1982) have reported that methyl mercury compounds account for an average of 30 percent of the total mercury in samples of natural waters from the Ottawa River in Canada and from river and sewage effluent samples in Japan. This is the only publication to date indicating the presence of a substantial fraction of methyl mercury in ambient water. Further work is necessary before general conclusions can be drawn.

Implications of these findings are not clear with regard to the composition of mercury in drinking water. Presently, the average daily human absorption of mercury from noncontaminated drinking water is estimated to be somewhat lower than 5 ng Hg/day. This is based on assumptions that the concentration of mercury in most drinking water is less than 25 ng Hg/l, two liters of water are consumed daily by the standard 70-kg adult, most mercury in noncontaminated drinking water is probably in the form of complexes of Hg^{++}, and gastrointestinal absorption of this form of mercury (Hg^{++}) is around 10 percent. Even if 30 percent of the total mercury is present as methyl mercury compounds, intake of the latter via drinking water would be negligible compared to intake from ingestion of fish and shellfish. At the present, the effect of water treatment, including chlorination, on various forms of mercury, is unknown.

The chemical form and concentration of mercury in fruit juices, soft drinks, alcoholic beverages, coffee, tea, and other drinks is not well described. It is unlikely that mercury concentrations will differ greatly from those in ordinary drinking water as mercury compounds are not known to be involved in the preparation or storage of these beverages.

3.3.4 Mercury in Food

The results of a number of extensive surveys (Swedish Expert Group, 1971; United Kingdom Department of the Environment, 1976; National Academy of Sciences, 1978) indicate that a major distinction should be drawn between fish, particularly the large carnivorous fish, and also shellfish and marine mammals on the one hand, and other flora and fauna on the other hand. In general, mercury concentrations in most vegetable and meat samples that have been tested are usually so low as to be near or below the limit of detection of mercury by most analytical methods. Thus, figures from surveys conducted by the U.S. Food and Drug Administration (Gartrell, 1984) indicate that most foodstuffs have total mercury levels of below 20 ng/Hg/g wet weight, although occasionally poultry and meat have been reported to contain levels of up to 200 ng/g wet weight. In view of the uncertainty of these generally reported low numbers, any calculations of average daily intakes from non-fish food merely represent crude estimates of mercury intake from such sources. Indeed, a low intake of mercury from non-fish sources is consistent with the finding that non-fish eaters have the lowest blood concentrations of mercury.

Analysis of fish tissue indicates that on the order of 70 to 90 percent of the total mercury is present as monomethyl mercury compounds (World Health Organization, 1976). Levels of methyl mercury in the larger predatory oceanic fish such as tuna and shark may reach values up to 5 ppm devoid of any direct contamination of the fish or the water by human activities (International Register of Potentially Toxic Chemicals, 1980). For example, over 50 percent of swordfish tested to date have values in excess of 1 ppm. Observations on canned tuna indicate average total mercury concentrations on the order of 0.24 ppm (Table 3-2).

In fresh water, the average concentration in most fish is below 0.2 μg/g; however, levels of mercury in pike may frequently exceed 1 μg/g, and values as high as 28 μg/g have been reported in heavily polluted areas (Fimreite and Reynolds, 1973). More details are available in a review by the United Nations Environmental Protection Program (International Register of Potentially Toxic Chemicals, 1980), in a large survey conducted in the United States on commercial species of fish (U.S. Department of Commerce, 1978), and in an extensive survey in England (United Kingdom Department of the Environment, 1976).

Some of the factors influencing the levels of methyl mercury in fish have been discussed briefly in the previous section. In addition to these factors, it should be noted that the concentration of methyl mercury in the aquatic system itself is a major contributing factor to levels of methyl mercury in fish. Two other controlling factors are the age and species of the fish.

Marine mammals can also accumulate mercury. For example, the livers of seals may, in some cases, contain very high concentrations of total mercury on the order of 340 μg/g, but over 90 percent of this is in the form of inorganic mercury which is probably combined in an inert form with selenium (Koeman et al., 1973). Nevertheless, sufficient amounts of methyl mercury are found in

TABLE 3-2. FISH AND SHELLFISH CONSUMPTION IN THE UNITED STATES (September 1973-August 1974)

	Rank	Amount, 10^6 lb/yr	Percent of total by weight	Number of actual users (millions)	Mean amount per user g/day	Aver.[c] mercury conc. ppm
Total		2957	100.0	197	18.7	
Tuna (mainly canned)	1	634	21.4	130	6.1	0.24
Unclassified (mainly breaded, including fish sticks)	2	542	18.4	68	10.0	0.21[d]
Shrimp	3	301	10.2	45	8.3	0.46
Ocean Perch[a]	4	149	5.0	19	9.7	0.13
Flounder	5	144	4.9	31	8.6	0.10
Clams	6	113	3.6	18	7.6	0.05
Crabs/lobsters	7	110	3.7	13	10.6	0.25
Salmon	8	101	3.4	19	6.7	0.05
Oysters/scallops	9	88	3.0	14	7.8	0.04
Trout[b]	9	88	3.0	9	12.3	0.42
Cod[a]	11	78	2.7	12	8.1	0.13
Bass[b]	12	73	2.5	7.6	12.0	0.21[e]
Catfish[b]	12	73	2.5	7.5	12.1	0.15
Haddock[a]	12	73	2.5	11	8.6	0.11
Pollock[a]	15	60	2.0	11	6.8	1.41
Herring/smelt						
Sardines	16	54	1.8	10	6.7	0.06
Pike[b]	17	35	1.2	2.5	17.4	0.61
Halibut[a]	18	32	1.1	5.0	8.0	0.33
Snapper	18	32	1.1	4.3	9.3	0.45
Whiting	20	25	0.9	3.2	9.7	0.05
All other classified		152	5.1			0.21

[a] Mainly imports.

[b] Fresh water.

[c] The geometric means.

[d] The value was assumed to be equal to the mean mercury concentration in all species reported by the U.S. Department of Commerce (1978), excluding the species reported in this table.

[e] Measurement values not available. Same assumptions made as in d.

Source: U.S. Department of Commerce (1978).

seal tissue, including liver, such that individuals consuming seal meat, like the Eskimo, have been shown to have high blood concentrations of methyl mercury (Galster, 1976).

The U.S. Department of Commerce (1978) conducted a survey of over 25,000 individuals, representative of the United States population, in order to determine the intake of methyl mercury from fish. On a per weight basis, it was found that consumption of tuna exceeds that of other species of fish in the United States (Table 3-2). However, since the actual number of users or consumers of tuna is also very high, the amount of tuna consumed per user is not dramatically different than the consumption per user of other species of fish. It is of interest to note that the highest consumption per user is of Northern pike, giving a value of 17.4 g/day, and that other species of freshwater fish -- bass, catfish, and trout -- are next highest per user consumption at about 12 g/day. Tuna falls more or less in the midrange, between 6 and 10 g/day. In fact, the range in per user consumption of different species is quite small, being no more than a factor of two, despite the huge range in total consumption of each species.

The data in Table 3-2 from the U.S. Department of Commerce (1978) do not allow for an accurate calculation of the average daily intake of fish, nor even for an accurate calculation of the range of daily intake. However, a rough estimate can be derived by dividing the total amount of fish consumed in the United States (top of column 3) by the total number of people consuming fish (top of column 5), resulting in a value of 18.7 g (top of column 6). This calculation is only a rough approximation of the average intake of fish since the distribution of individual consumption is not known. Similarly, a rough calculation of average mercury consumption may be made in the same way. Using the figures for amount consumed of each species of fish (column 3) and the average concentration in each species (column 7), total intake of mercury from all species of fish for the entire population may be calculated. By dividing the total mercury intake by the total number of consumers (197 million, top of column 5), a value of 4.7 μg Hg/day is obtained. It should be emphasized that this calculation is very speculative and it assumes all factors affecting fish consumption and mercury levels in fish are randomly distributed.

Fouassin and Fondu (1978) have calculated that, in Belgium, the intake of mercury due to fish consumption is 2900 ng Hg/day. Bernhard and Andreae (1984) estimated an average adult human intake worldwide of 2 μg Hg/day from seafoods.

Previously, Clarkson and Shapiro (1971) had presented calculations indicating an intake of methyl mercury for U.S. adults of 3 μg Hg/day based on blood levels.

The average consumption of fish given in Table 3-2 as 18.7 g fresh weight per day compares with a reported value of 16 g/day from the Food and Agriculture Organization (FAO, 1980) of the United Nations. However, it should be noted that considerable national and individual differences must exist. Populations largely dependent on fish as a source of protein have average daily intakes of up to 193 g fresh weight (FAO, 1980). Canadian Indians have been reported to take in as much as 1300 g/day during the fishing season (Piotrowski and Inskip, 1981). These native populations live in villages close to large freshwater fishing areas and have very high intakes of freshwater fish that tend to be high in the food chain, such as pike, walleye, and bass. Intake of methyl mercury in the special population groups having unusually high intake of fish, may be 10 to 100 times greater than that in the general population.

3.3.5 Relative Contributions of Various Media to Human Exposure

The three major media contributing to human intake of mercury are air, drinking water, and food. In considering human intake, it is most important to treat each major chemical species of mercury separately. Of greatest concern are metallic mercury vapor (Hg^o), compounds of inorganic mercury (Hg^{++}) and compounds of methyl mercury (CH_3Hg^+). The relative contribution of these species to mercury intake is presented in detail in Table 6-1 (Chapter 6).

Air is the only source of human exposure to Hg^o. People living in non-polluted rural areas would absorb about 16 ng Hg/day/adult as compared to about 160 ng Hg/day/adult absorbed by individuals living in cities. It is highly unlikely that average daily intakes over the long term would exceed 800 ng Hg/day/adult. Drinking water only contributes marginally to human daily intake, resulting in probably no more than 5 ng Hg/day. While the chemical form of mercury in drinking water is not totally established, most is thought to be in the form of Hg^{++} If all were in the form of Hg^{++} compounds, probably not more than 10 percent would be absorbed into the bloodstream (See Chapter 4). It is possible, however, that up to 30 percent may be present as methyl mercury compounds, in which case the percentage absorbed would be considerably higher. However, by far the predominant source of human exposure to methyl mercury compounds is fish and fish products. In Section 3.3.4, based on data in Table 3-2, it was calculated that the average intake for an adult in the United States is 4700 ng Hg/day. This is a speculative number in view of the assumptions that had to be made in the calculation of the number, but this value compares reasonably well with other estimates for worldwide intake (2000 ng Hg/day) and for intake measured in an industrialized European country (2900 ng Hg/day) and a previous estimate for the U.S. population (3000 ng Hg/day).

3.4 SUMMARY

Mercury exists in three oxidation states -- Hg° (metallic), Hg_2^{++} (mercurous) and Hg^{++} (mercuric) mercury -- and a wide variety of chemical forms, the most important being compounds of methyl mercury, mercuric mercury, and the vapor of metallic mercury. Mercury forms stable organometallic compounds in which the mercury atom is covalently bound to one or more carbon atoms.

The global cycle of mercury involves the emission of Hg° from land and water surfaces to the atmosphere, transport of Hg° in the atmosphere on a global scale, possible conversion of unidentified soluble species, and return to land and water by various depositional processes. The ultimate deposition of mercury, probably as HgS, is believed to be in ocean sediments.

Inorganic mercury undergoes methylation by microorganisms that are widespread in bodies of both fresh and ocean water and probably in soils. Methyl mercury is avidly accumulated by fish and attains highest concentrations in large predatory fish at the top of the aquatic food chain. By this means, it enters the human diet. Certain microorganisms can demethylate CH_3Hg^+; others can reduce Hg^{++} to Hg°. Thus, microorganisms are believed to play an important role in the fate of mercury in the environment and in affecting human exposure.

Man's contribution of Hg° to the atmosphere is believed to range from 10 to 80 percent of total input with estimates presented within this chapter of at least 20 percent. The burning of fossil fuels is an important anthropogenic source. Background levels in the troposphere of the Northern Hemisphere are now estimated at 2 ng Hg/m^3. In regionally polluted areas, values lie between 3 to 4 ng Hg/m^3. Urban air may have average concentrations up to 10 ng Hg/m^3. Most of the mercury in the atmosphere is probably in the form of Hg°.

Mercury in drinking water is usually in the range of 5 to 100 ng Hg/l with an average value of about 25 ng Hg/l. The forms of mercury in drinking water are not well studied, but Hg^{++} is probably the predominant species present as complexes and chelates with ligands in water.

Concentrations of mercury in most foodstuffs are often below the detection limit (usually 20 ng Hg/g fresh weight). Fish and fish products are the dominant source of mercury in food, mainly in the form of methyl mercury compounds (70-90 percent of the total). The average concentrations in edible tissues of various species of fish cover a wide range, from 50 to 1400 ng Hg/g fresh weight. Large predatory freshwater fish, such as Northern pike (610 ng Hg/g fresh weight) and trout (450 ng Hg/g fresh weight), have some of the highest average concentrations.

The atmosphere is the only source of human exposure to Hg^o. The daily amount absorbed into the bloodstream by adults is about 16 ng Hg in rural areas and about 160 ng Hg in urban areas. Drinking water supplies somewhat under 25 ng Hg/day, only a small fraction of which is absorbed into the bloodstream. Intake of fish and fish products results in the average daily absorption of amounts of methyl mercury variously estimated to be between 2000 to 4700 ng Hg. The absorption of inorganic mercury from foodstuffs is difficult to estimate because levels of total mercury are close to the limit of detection in many food items and the chemical species of mercury have not usually been identified.

The intake of total dietary mercury has been measured by the United States Food and Drug Administration (Gartrell, 1984) over a number of years for various age groups. The average daily intake over the period 1973 to 1982 has been in the range of 2000 to 7000 ng Hg for adults and up to 1000 ng Hg for toddlers and infants. The most recent figures (fiscal year 1981-82) were 3000 ng Hg for adults, 1000 ng Hg for toddlers, and less than 1000 ng Hg for infants. These figures support the conclusion that fish and fish products are the major source of total mercury in the diet.

4. PHARMACOKINETICS AND BIOTRANSFORMATION IN MAN AND ANIMALS

4.1 VAPOR OF METALLIC MERCURY

In 1973, a Task Group on Metal Accumulation made the following recommendations:

> "Indices of metal accumulation and exposure are urgently needed. It has been shown that metal levels in available biological material (blood, urine, hair, etc.) might give an approximate indication on recent exposure but with few exceptions cannot be used to calculate metal concentration in critical organs or in whole body. Consequently, in many cases, it is impossible to tell on the basis of sample analysis whether accumulation in the critical organ is progressing and how far metal concentration in the critical organ is from the critical level. The reason for this lack of knowledge is two-fold. One is the lack of proper numerical values which could be set up in an equation; the other is the lack of a proper mathematical model which is adequate to describe with approximate accuracy the complexity of metal accumulation in the body."

A World Health Organization environmental criteria document (1976) made special note that this information was lacking in the case of inhaled mercury vapor.

Although the literature does not contain sufficient information from which to construct a satisfactory compartmental model, a review of the field reveals important findings that should be incorporated into a complete scheme. These findings are summarized and discussed below.

4.1.1 Routes of Absorption

4.1.1.1 Lung--About 80 percent of the inhaled mercury vapor is retained in body tissues as evidenced by observations on both animals and man (Teisinger and Fiserova, 1965; Nielson-Kudsk, 1965b). Teisinger and Fiserova (1965) originally proposed that the vapor was absorbed across the walls of the bronchioles and larger airways of the lung, but subsequent evidence points strongly to the alveolar region as the predominant site of absorption into the bloodstream (Berlin et al., 1969a). During the absorption process, mercury becomes deposited in lung tissue, as evidenced by animal experiments and by observations in volunteers inhaling a tracer dose of mercury (Berlin and Johansson, 1964; Hursh et al., 1976).

4.1.1.2 Skin--Studies in the early part of the century indicate that absorption of mercury can take place across the skin of man (Juliusberg, 1901) and animals (Schamberg et al., 1918) when exposed to metallic mercury. It is surprising that no further studies have been reported since droplets of metallic mercury in footwear and clothing probably come into contact with skin during occupational exposure. Most reports on air concentrations of mercury vapor and corresponding concentrations in samples of blood and urine have not taken into account possible absorption across the skin from contact with droplets of metallic vapor and from high concentrations of vapor trapped in the footwear. While it has been proposed that, on an individual basis, such contact may contribute to overall mercury absorption (see section 6.3.1.1 for a discussion of the importance of microenvironmental exposure), it is presently not known whether mercury would be directly absorbed from the droplets, or whether mercury vapor, formed from the droplets, would be absorbed.

4.1.2 Deposition and Retention

Mercury distributes to all parts of the body following inhalation of mercury vapor. A general picture of distribution, deposition and elimination from tissues is indicated in Figure 4-1. The data are based on regional and whole-body counting of volunteers who inhaled, over a period of 20 minutes, air containing 0.1 mg Hg/m^3 labelled with a radioactive isotope. As can be seen from the figure, the kidney accumulated the highest concentration of mercury. Distribution of mercury appeared to be complete within 24 hours for most regions of the body except for the head, where peak radioactivity was not attained until two to three days later. Elimination from the whole body and kidney region took place at about the same rate. Clearance from the head region was more rapid than from most other areas of the body with an elimination half-time of about 20 days (Table 4-1). Decline in radioactivity in the chest region was biphasic. A rapid component, attributed by Hursh et al. (1976) to mercury deposited in lung, had an elimination half-time of about 2 days. A slower component, half-time similar to kidney and whole body, was attributed to radioactivity in other tissue in the chest region. Experiments in non-human primates confirm the finding that mercury clearance from lung is more rapid than from other tissues (Berlin et al., 1969a).

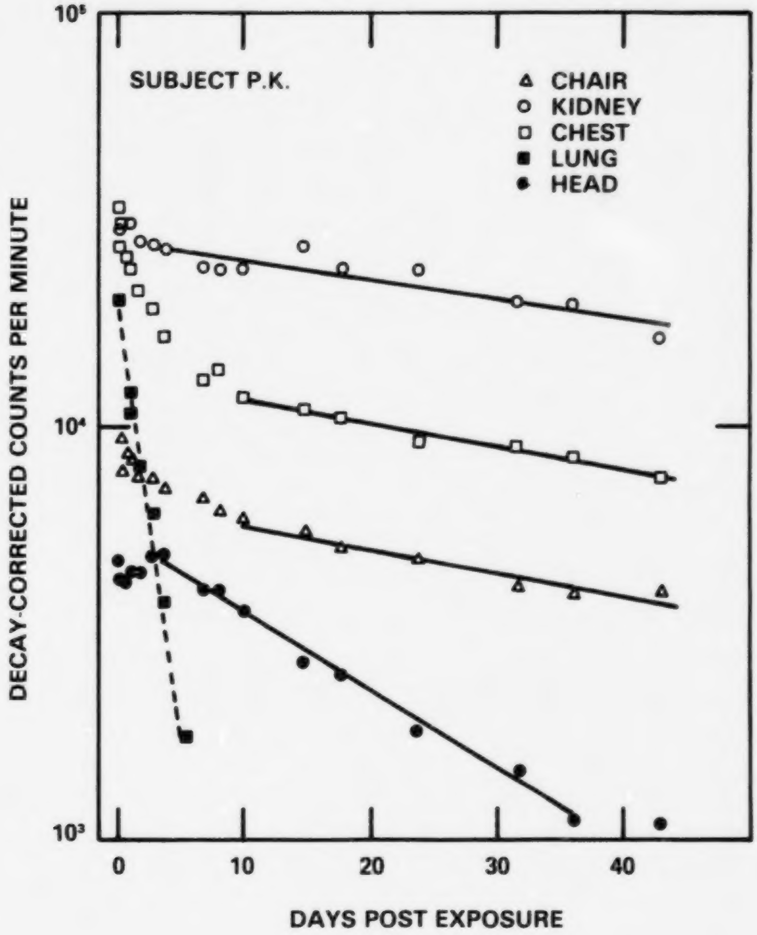

Figure 4-1. Decay-corrected rates for four positions of crystal detector plotted as a function of days after exposure. Points for the lung (dotted line) are generated by extrapolating the straight line for the chair position to zero time and plotting the difference between values on this line and the measured data points. The chair postion is the position assumed by the subject such that the recorded radiographic counts most closely correspond to the total body burden of the subject.

Source: Hursh et al. (1976).

TABLE 4-1. SUMMARY OF HALF-TIMES OF MERCURY IN HUMAN TISSUES

Tissue	Exposure Conc. (mg/m^3)	Duration	First Component % deposited	First Component T 1/2 (days)	Second Component % deposited	Second Component T 1/2 (days)
Blood[a]	0.1	20 min	>60	3.3	not detected[b]	
Blood[c]	>>0.1	few hours	~90	~2.0	~10	20
Blood[c]	~0.05	months	?	?	~100	30
Lung[d]	0.1	20 min	~100	1.7	not detected[b]	
Kidney[d]	0.1	20 min	~100	64.0	not detected[b]	
Head[d]	0.1	20 min	~100	21.0	not detected[b]	
Whole Body[d]	0.1	20 min	~100	58.0	not detected[b]	

[a] Cherian et al., 1978.

[b] Other components having longer half-times cannot be excluded but would account for small fraction of the total.

[c] Clarkson, 1978.

[d] Hursh et al., 1976.

Autoradiographic studies (Berlin and Ullberg, 1963b; Berlin and Johansson, 1964; Berlin et al., 1966) indicate that after inhalation of mercury vapor, mercury distributes preferentially to certain types of cells. Mercury, whether administered as Hg^{++} or converted in the body to Hg^{++} from inhaled Hg^{o}, has a special affinity for ectodermal and endodermal epithelial and glandular cells. Thus, mercury is seen to be accumulated in the mucosa of the intestines, in epithelial cell layers of the skin and in glandular tissue such as salivary, pancreas and sweat glands, in the kidneys, and in epithelial-type organs such as testes and prostate.

Deposition and clearance in blood, brain, kidney, and fetal tissue are discussed in more detail below in view of their importance in the metabolism and toxicity of inhaled mercury.

4.1.2.1 Blood--Cherian et al. (1978), in studies on volunteers exposed for 20 minutes to a tracer dose of radioactive mercury vapor, reported that approximately 2 percent of the absorbed dose was deposited in one liter of whole blood after initial distribution was completed. Uptake in the red cell compartment was complete within a few hours, but plasma uptake reached a maximum in about one day. The concentration of mercury in the red cells was about twice that in plasma, a relationship that persisted for at least six days after exposure. Cherian et al. (1978) also reported a mean half-time in blood of 3.3 days in volunteers exposed for 20 minutes to a tracer dose of radioactive mercury vapor (Table 4-1). This half-time accounted for the loss of at least 50 percent of the radioactive mercury from blood. Red blood cells and plasma had similar half-times. However, blood and excreta were only followed for about 5-7 days due to counting problems encountered in working with a short-lived isotope. As a result, blood mercury levels and excretion rates were still changing at the end of the 7-day period due to distributional phenomena. This observation was supported by the fact that whole body counts, measured in the chair position (a measure of whole-body radioactivity) did not go into a terminal decay phase until after approximately 9 days and may even have been developing a slower component after 30 days.

An accidental mercury vapor exposure of a family in Boston (Figure 4-2) has supplied some additional information concerning blood half-times (Clarkson, 1978). The major portion of the exposure probably occurred within a half-hour period, with a smaller, protracted exposure over the duration of an evening. It appears that there was an early, rapid decline over the first few days post-exposure, and, by about days 5-7, the mercury in blood was decreasing with an

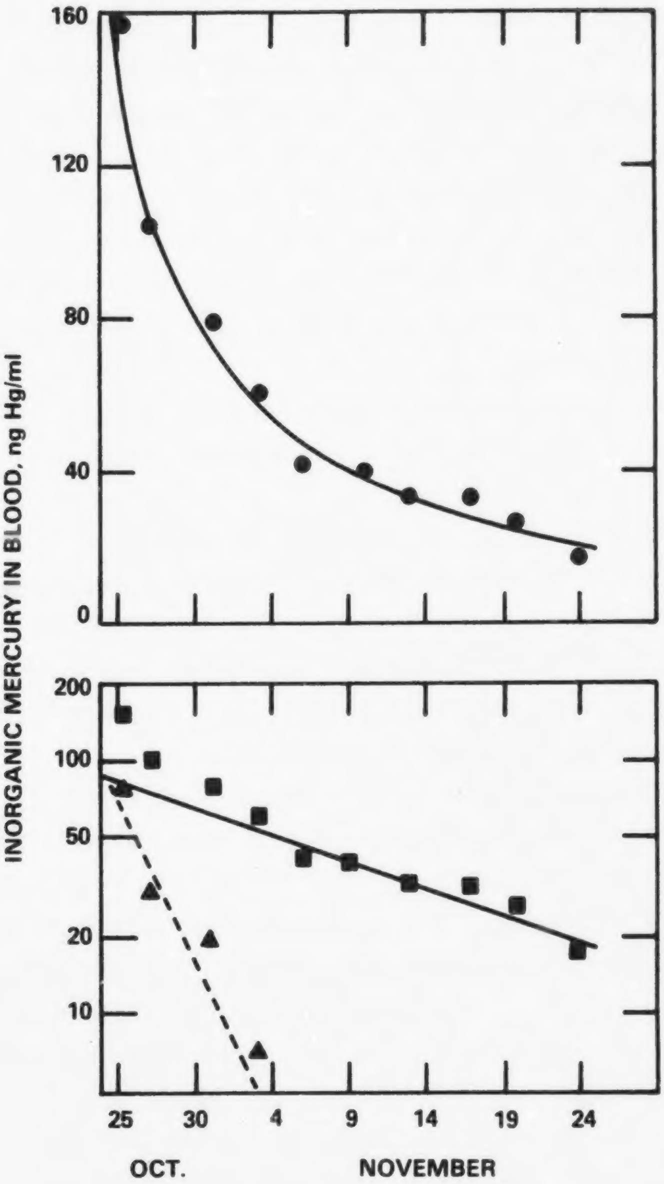

Figure 4-2. The fall in mercury concentrations in blood in two adult females following a brief exposure (less than 3 hr) to mercury vapor. Upper graph has a linear scale on the ordinate. The lower graph has a logarithmic scale and curve stripping procedures were used to estimate a component with the different half-time (slow component, 14.9 days; fast component, 2.4 days).

Source: Clarkson (1978).

approximately 15-day half-time, which was maintained for the remainder of the first month post-exposure. A 7-month period lapsed before the next samples were collected, and by that time the blood levels were down to the 6-11 ng/ml range, which is in the vicinity of a high normal background level.

Another family exposure to mercury vapors involved a husband and daughter who were exposed for 6 to 8 months in the home; the wife had experienced a prior exposure of about 18 months in her workplace (Clarkson, 1978). Samples of blood were collected starting about 1 month after cessation of exposure. Therefore, an early rapid fall in concentration due to short half-time components was missed. The blood concentration of mercury in the wife declined with a half-time of 30 days. The other two family members had longer half-times, but their blood levels were sufficiently low that dietary mercury might have influenced the results.

If the mercury in the body is all in exchangeable pools, one would anticipate a protracted half-time in the blood to agree with the protracted whole-body retention half-times of 40-60 days (Hursh et al., 1976; Rahola et al., 1973). The observation of a 30-day half-time is consistent with the findings of Rahola et al. (1973), who reported slow components for red cells of 13-42 days following the oral administration of an inorganic mercury salt, but it is less than the whole-body half-times reported by Hursh et al. (1976). However, if there is sequestration, such a protracted blood half-time will not be observed if the sequestered mercury is cleared into the excreta directly.

4.1.2.2 Brain.--As shall be discussed later, inhaled mercury vapor is rapidly oxidized in blood and other tissues to the divalent form (Hg^{++}). This is consistent with the finding that the general pattern of deposition in organs and tissues after exposure to mercury vapor is essentially similar to that pattern seen when divalent salts of mercury, such as mercuric chloride, are given to animals parenterally (Rothstein and Hayes, 1960; Hayes and Rothstein, 1962). However, the amount deposited in the brain is about ten times greater in the case of exposure to mercury vapor as compared to similar doses of ionic mercury (Berlin and Johansson, 1964). Although these observations are from animal experiments, the fact that similar results are seen in several different species strongly suggests that the same situation might apply to man (Berlin et al., 1969b). Volunteers inhaling radioactive mercury accumulate about 7 percent of the dose in the head region, consistent with diffusion into the brain (Hursh et al., 1976).

Experiments in mice given a 4-hour exposure indicated a longer retention time in brain than in other tissues (Berlin et al., 1966). The amount deposited in the brain has been reported for a variety of species and is approximately similar when expressed on a per gram tissue basis. The amount deposited is usually between 0.2 and 1 percent of the dose per gram tissue. A notable exception to this observation is in a report by Magos (1967), where it was noted that as much as 6 percent was deposited in the brains of mice used in his study. The results suggest an important strain difference in the mice used by Magos, although the lower body weight of his mice might account for some of the difference. It is noteworthy that it was in this same strain of mice that Magos reported a long biological half-time of mercury in the brain versus other tissues.

Autoradiographic studies of central nervous system tissue in mice and rats exposed to radioactive mercury, 6 hours daily, for 10 days, and killed at intervals of up to 60 days after exposure, indicate that more mercury is accumulated in gray matter than white matter (Cassano et al. 1966, 1969). The highest concentrations of radioactivity were found in the cerebellum and brain tissue stem nucleii. In the cerebellum, the greatest accumulation was in the cytoplasma of the purkinje cells. High concentrations were seen in periventricular structures and other tissues in close contact with cerebrospinal fluid. Berlin and Ullburg (1963a) suggested that cerebrospinal fluid may be an important route of entry into the brain. However, the data are also consistent with the premise that blood is the major entry portal of mercury into the brain and that cerebrospinal fluid is the major exit pathway.

Hursh et al. (1976) observed a 21-day clearance half-time (Table 4-1) from the head, following a brief vapor exposure to humans. This half-time was observed over a 40-50 day post-exposure period and is in the range of observed half-times for blood. The peak value of the head counts came near the peak time for the plasma, raising the question of whether or not the brain levels were following the plasma. However, for the subject cited, the change between the last two counting days was not as great as expected, which raises the possibility that some material was either being sequestered in the brain or at least was being cleared at a considerably slower rate. Indeed, Takahata et al. (1970) and Watanabe (1971) reported that mercury persists in brain for many years following the cessation of occupational exposure to mercury vapor, and Berlin (1976) noted that mercury concentrations in brains of squirrel monkeys continued to increase after two months of exposure.

In the above considerations regarding the relationship between dose and brain mercury content, Henderson et al. (1974) have noted the potential importance of rate of dosage of mercury vapor in view of the conversion of Hg^o to Hg^{++} by the red blood cells. They suggest that higher rates of mercury vapor intake might lead to a greater fraction of inhaled vapor reaching the blood-brain barrier as Hg^o than would lower rates of intake (see Section 4.1.4.3).

4.1.2.3 Fetus--No quantitative data are available on the rate of transfer of inhaled vapor to the fetus in humans. When pregnant rats received a 15 minute exposure to radioactive vapor on day 17 of gestation, the amount of mercury was 4 times greater in the fetuses from these dams as compared to fetuses from mothers given an equivalent dose of $HgCl_2$ (Clarkson et al., 1972). In this study, the fetuses were examined immediately after exposure. Dencker et al. (1983) reported that, after 60-minute exposures of mice to mercury vapor, more mercury was accumulated by the fetus at later stages of gestation. Pretreatment of the mother with a large dose of ethanol (2 g/kg) increased the total mercury accumulation in the fetus by about fourfold (Khayet and Dencker, 1982). No information is available on long-term exposures.

In two cases of exposure of pregnant human females to mercury vapor, it was found that the concentration of mercury in infant's blood was similar to that in the mother's blood at the time of delivery (Clarkson, 1978).

4.1.2.4 Kidney--The overall pattern of deposition in the body is dominated by accumulation in kidney tissue. Concentrations in kidney are several orders of magnitude higher than in other tissues following both single and repeated exposures (Hayes and Rothstein, 1962; Rothstein and Hayes, 1964). In the experiments of Hayes and Rothstein, the amount of mercury accumulated in kidney accounted for as much as 90 percent of the total body burden. The retention of this large amount of mercury in the kidney may be of considerable significance in assessing potential toxic hazard, as will be discussed below.

Some agents that tend to reduce mercury levels in kidney tissue increase mercury concentrations in all other tissues. This has been discussed in detail by Magos (1973), who cited examples of a number of chemicals that would reduce kidney concentrations and elevate mercury throughout the rest of the body. Thus, important factors affecting the toxicity of inhaled mercury vapor might be those processes or conditions which lead to diminished renal uptake of mercury.

Sexual dimorphism may also affect metabolism. Shaikh (1981, 1983) has reported that concentrations of mercury are greater in male mice and rats exposed to mercury vapor than in females similarly exposed.

Observations in humans (Cherian et al., 1978) and in rats (Gage, 1961) are consistent with the observed pooling and probable sequestration of mercury in the kidney. It therefore seems plausible to assume that the urinary excretion rate of mercury should not be simply proportional to the plasma level but should also include a term proportional to the kidney level. It is also entirely possible, as suggested by Gage's data, that the kidney consists of more than one compartment, which would further add to the complexity of the system.

4.1.3 Excretion

Urine and feces are the main pathways of excretion after exposure to mercury vapor, although exhalation of vapor and excretion in saliva and sweat may contribute to overall excretion (Lovejoy et al., 1974; Joselow et al., 1968). Animal data indicate that, shortly after exposure, the gastrointestinal tract is the predominant pathway of excretion, but, as the kidney becomes more and more the predominant site of storage of mercury, urinary excretion takes over (Rothstein and Hayes, 1964). In humans, following a brief exposure, urine accounted for 13 percent of the total urine and fecal excretion, but, after long-term occupational exposure, urine accounted for 58 percent (Table 4-2). In tracer experiments in volunteers it was noted that the specific activity of mercury in urine was unrelated to and significantly lower than the specific activity in plasma (Cherian et al., 1978). This observation suggests that urinary mercury originates from a large pool of mercury in kidney as opposed to glomerular filtration of plasma mercury. However, this conclusion is valid only if the plasma activity reflects the filterable fraction.

In volunteers exposed to mercury vapor, it was found that approximately 7 percent of the inhaled dose would eventually be excreted via exhalation in the expired air. Most of the exhalation was completed within one week and constituted approximately 37 percent of total mercury excretion during the same period (Table 4-2). If the reduction reactions in the body (see below) are sufficiently rapid to maintain equilibrium between mercury vapor and the oxidized form in the blood and tissues, both the exhalation of vapor over a longer period than that observed by Hursh et al. (1976) and, consequently, a

TABLE 4-2. THE RELATIVE AMOUNT OF MERCURY EXCRETED IN URINE, FECES, AND EXPIRED AIR AFTER EXPOSURE TO MERCURY VAPOR

Excretion medium	Type of exposure	Percent of total excretion
Expired air	Short-term[a]	37
Urine	Short-term[a]	13
Feces	Short-term[a]	50
Urine	Long-term[b]	58
Feces	Long-term[b]	42

[a] Average excretion in the first week following exposure to 0.1 mg Hg/m^3 for a 20 minute period (Hursh et al., 1976; Cherian et al., 1978).

[b] The daily excretion in urine and feces was measured in individuals exposed for several years to 0.05 to 0.2 mg Hg/m^3 (Tejning and Ohman, 1966). Information on excretion by other routes was not available.

greater than 7-percent excretion by that pathway would be expected. However, the increment may not have any overall significance.

From the work of Gay et al. (1979), it has been shown that mercury from tooth fillings can increase the amount of mercury expired in air. After 15 minutes of chewing, people with no fillings expired from 1 to 6 ng Hg/10 breaths, whereas people who had their teeth filled one to two years prior to testing, expired from 17 to 76 ng Hg/10 breaths. People with teeth filled within one to two weeks prior to testing expired between 172 to 244 ng Hg/10 breaths. Prior to chewing, expiration of mercury did not exceed 22 ng Hg/10 breaths irrespective of the time after an individual's teeth were filled. The significance of these findings to potential human health effects is wholly unknown.

Quantitative information on excretion via sweat and saliva is not available. In workers experiencing profuse perspiration, amounts of mercury excreted in the sweat may exceed those in the urine (Lovejoy et al., 1974).

A highly schematic and simplified version of processes that might be operative in the transport of mercury from inspired air to various tissues is given in Figure 4-3. The roles of three of the major processes instrumental in this transport are discussed below. Each has been dealt with separately for convenience of presentation, but it must be recognized that considerable interaction must occur between them.

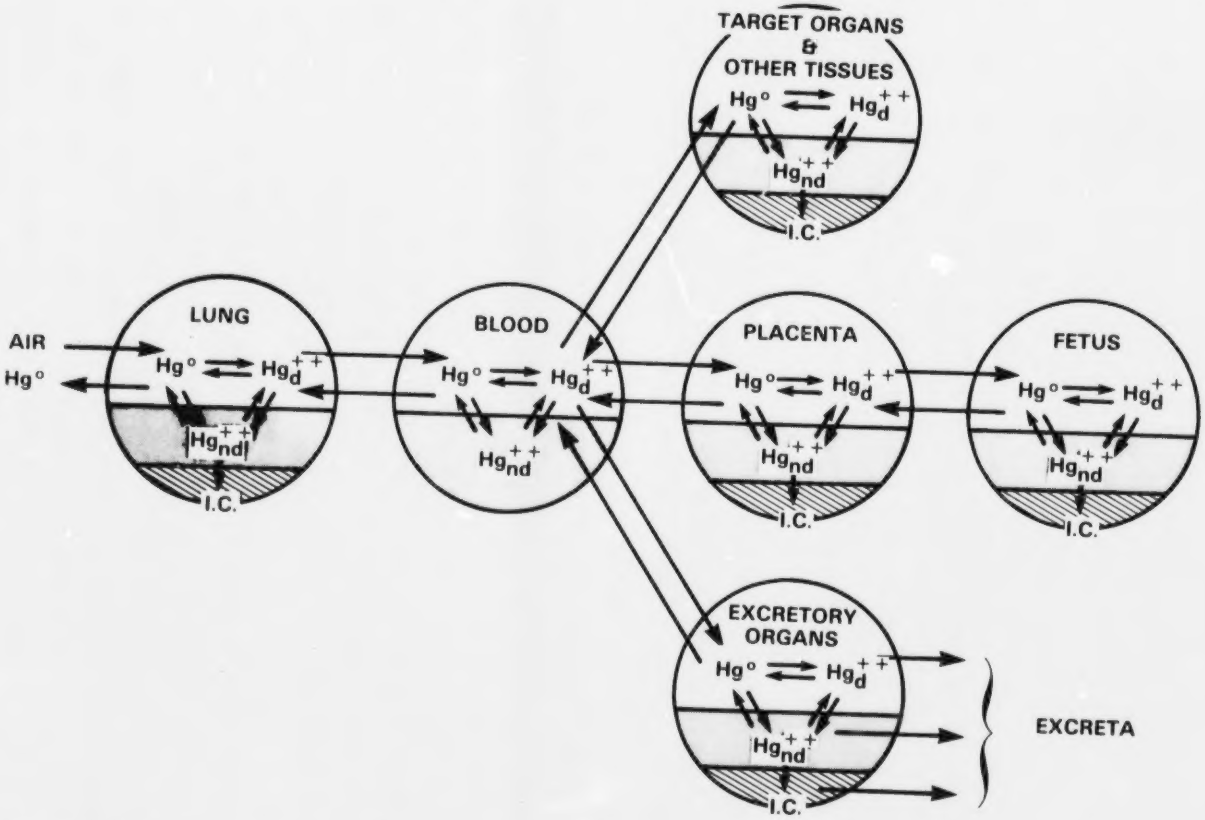
TARGET ORGANS & OTHER TISSUES
AIR
Hg°
LUNG
BLOOD
PLACENTA
FETUS
EXCRETORY ORGANS
EXCRETA
Hg°
Hg_d^{++}
Hg_{nd}^{++}
I.C.

Figure 4-3. A schematic representation of the fate of inhaled mercury vapor. The symbols have the following significance:

Hg° - mercury vapor
Hg_d^{++} - divalent mercury present as diffusible complexes and chelates
Hg_{nd}^{++} - divalent mercury in a non-diffusible form and in equilibrium with Hg_d^{++}
I.C. - inert complexes of mercury

The blood compartment should be represented as two subcompartments — plasma and cells. As discussed in the text, the distribution of mercury favors the cell compartment after exposure to mercury vapor, whereas after doses of inorganic mercury salts, the distribution is more or less equal.

4.1.4 Biotransformation, Speciation and Transport

4.1.4.1 Biotransformation--Studies on human blood exposed *in vitro* to mercury vapor have indicated that the vapor becomes oxidized to the divalent form (Hg^{++}). The reaction takes place principally, if not solely, in the blood cells. The process occurs via the hydrogen peroxide catalase pathway where monatomic mercury is oxidized by catalase complex I in a peroxidative reaction believed to be similar to other peroxidative reactions by catalase (Halbach and Clarkson, 1978). The process of oxidation by red cells can be greatly accelerated by the infusion of hydrogen peroxide into the red cell suspension or by the use of such agents as methylene blue that enhance endogenous hydrogen peroxide production. The process can be inhibited by low concentrations of ethanol, which presumably act as a competitive substrate. Other alcohols that are substrates for the peroxide reaction inhibit the uptake of mercury vapor by red cells (Nielsen-Kudsk, 1973). The importance of the oxidation step in the retention of inhaled vapor and its deposition in the bloodstream is demonstrated by observations on the effects of alcohol. For example, Nielsen-Kudsk (1965a) showed that workers who had ingested a moderate dose of alcohol retained about 50 percent less vapor than workers not ingesting alcohol. The deposition in blood was dramatically reduced when volunteers took alcohol before being exposed to mercury vapor. This evidence is presented in Figure 4-4 where it may be seen that the deposition of mercury in the red cells was reduced almost by a factor of ten in individuals having alcohol blood levels less than 8 mg percent. However, all the observations to date on both animals and man have been concerned with single or brief exposures to vapor and alcohol. No information is available on the role of repetitive dosing with alcohol in animals or man continually exposed to mercury vapor.

That oxidation of mercury occurs in the lung tissue is suggested by the fact that treatment of animals with ethanol dramatically reduces the amounts of mercury deposited in lung tissue after brief exposures to vapor (Magos et al., 1973). Lung deposition was also reduced by ethanol in humans exposed to tracer doses of mercury vapor (Hursh et al., 1980).

Oxidation of mercury vapor in liver tissue is suggested by the fact that treatment of animals with alcohol can drastically change the uptake by the liver. Observations on homogenates of rat liver indicate that mercury is readily oxidized and that the hydrogen peroxide catalase pathway is the predominant pathway of oxidation (Magos et al., 1978). The oxidational capacity

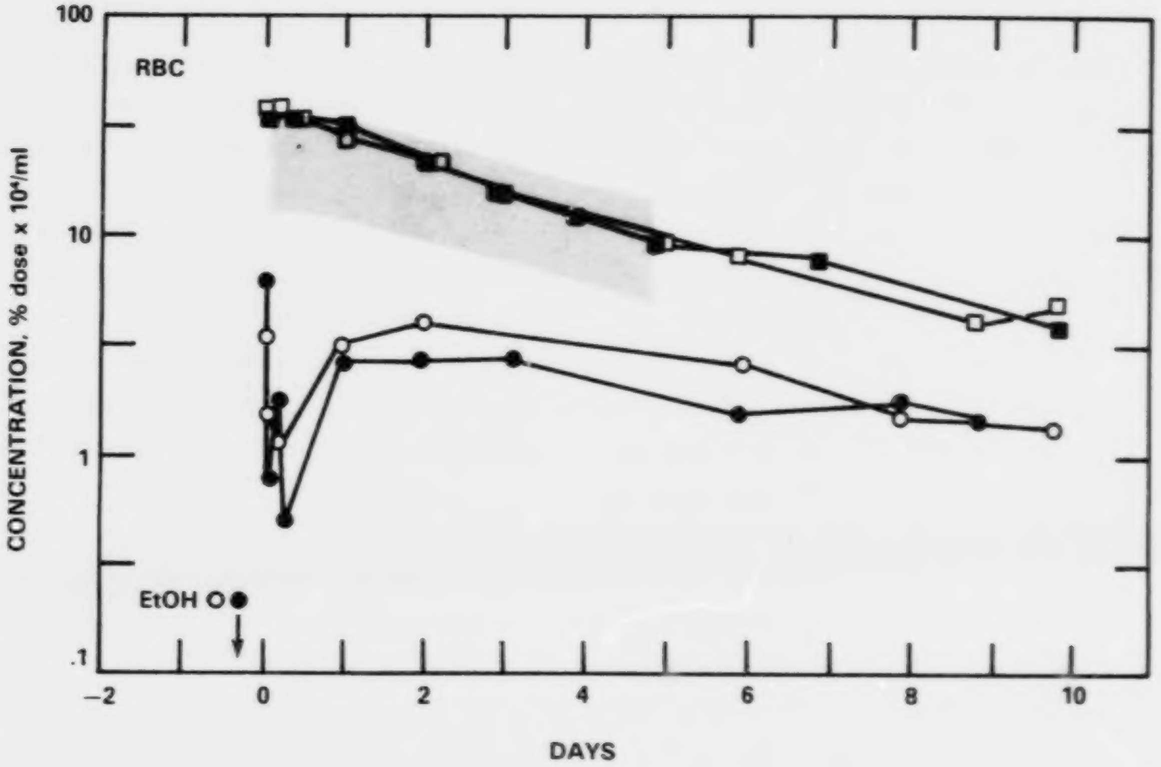

Figure 4-4. The deposition and retention of mercury in red blood cells in volunteers inhaling a tracer dose of mercury vapor. Ethanol (EtOH) was consumed 20 minutes prior to exposure to mercury vapor. The maximum blood concentrations were about 80 mg%. The shaded area covers the range of mercury concentrations in five subjects not taking ethanol. Two other subjects (□ and ■) did not take ethanoi and were observed for a longer period (10 days) than the other control group. Exposure to vapor (0.1 mg Hg/m^3) was for approximately 20 minutes.

Source: Adapted from Hursh et al. (1980).

is so great that, under *in vitro* conditions, the rate of delivery of mercury vapor to the homogenate appears to be rate-determining in the uptake process. This may also be true in the intact animal. Thus, treatment of animals with alcohol actually produces a large increase in deposition of mercury in the liver following brief exposure to mercury vapor (Magos et al., 1973). Alcohol, by inhibiting oxidation in blood, allows more vapor to be carried to the liver where the large reserve of catalase complex I is able to readily oxidize this increased supply of vapor. Autoradiographic studies by Dencker et al. (1983) support this interpretation.

The extent to which oxidation and reduction processes are occurring either in the placenta or in the fetus has not yet been thoroughly studied. The autoradiographic findings of Dencker et al. (1983) suggest that oxidation is taking place in fetal liver tissues.

Recently, evidence has come to light that the divalent (oxidized) form of mercury is subject to reduction in mammalian tissues. This is evidenced by the finding that exhalation of vapor occurs in mice and rats treated parenterally with mercuric chloride (Clarkson and Rothstein, 1964; Dunn et al., 1978, 1981b; Sugata and Clarkson, 1979). Ethanol is able to elicit a tenfold increase in the exhalation of vapor in volunteers exposed briefly to mercury vapor (as shown in Figure 4-5). More recently, ethanol has been shown to elicit exhalation of vapor in volunteers given tracer doses of mercuric chloride (Clarkson, 1978) and to increase exhalation of vapor in mice dosed parenterally with mercuric chloride (Dunn et al., 1981b). It is not known to what extent this reduction process applies to all tissues in the body; however, it is known that mercury will volatilize from liver and kidney homogenates of animals given divalent mercury and that the volatilization rate is increased by adding ethanol to the homogenate (Dunn et al., 1981a).

The effect of alcohol in increasing volatilization of mercury *in vitro* and *in vivo* is probably due to its inhibitory action on the oxidation step, thus, preventing the reoxidation of the vapor. This proposed mechanism is supported by the finding that other inhibitors of catalase also increase volatilization of mercury (Sugata and Clarkson, 1979; Dunn et al., 1981a).

The enzyme responsible for reduction of mercury has not yet been identified. Glutathione reductase is a distinct possibility in view of the finding by Williams et al. (1982) that this enzyme is similar in structure to mercuric ion reductase in microorganisms. If this proves to be the case, ethanol may

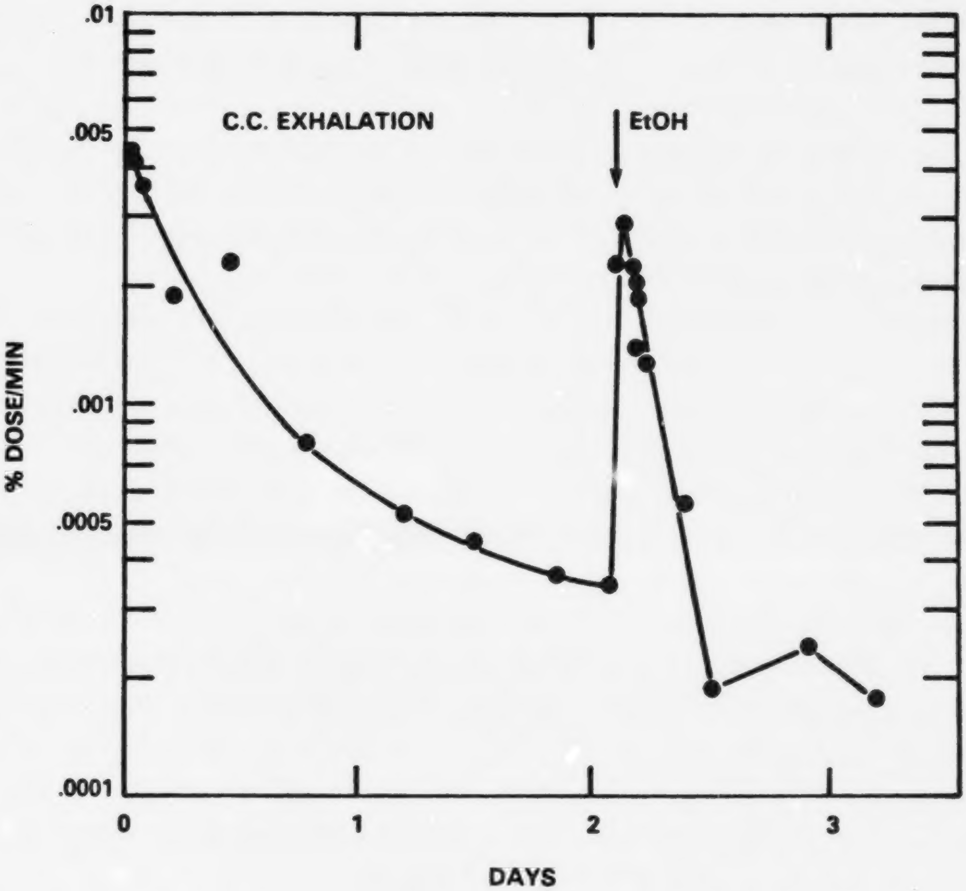

Figure 4-5. The rate of exhalation of mercury from a volunteer who received a brief (20 min) exposure to mercury vapor labeled with the ^{203}Hg isotope. Alcohol was consumed at 48 hours after the exposure to vapor in an amount that increased blood alcohol concentration to about 80 mg%.

Source: Hursh et al. (1980).

directly enhance the reduction process. The reduction of Hg^{++} by bacterial reductase requires NADPH as follows:

$$Hg^{++} + NADPH + H^{+} \longrightarrow Hg^{0} + NADP^{+} + 2H^{+}$$

The metabolism of ethanol to acetaldehyde could provide NADPH for this conversion. However, oxidation of alcohol occurs almost entirely in liver tissue and, therefore, would not provide NADPH for volatilization observed in kidney slices.

In summary, an oxidation-reduction cycle for mercury exists in mammalian cells. Mercury in the zero oxidation state, Hg^{0}, is probably the more mobile species, whereas divalent mercury, Hg^{++}, is the more reactive species inasmuch as it will more avidly bind to tissue ligands. The recently discovered cycle, mediated by at least two enzyme systems, is probably of profound importance in the toxicology of inorganic mercury.

The oxidation-reduction cycle may also play a role in the metabolism of alkylmercury compounds. It has been shown that mice dosed with methyl mercury exhale mercury vapor and that ethanol increases the rate of this exhalation (Dunn and Clarkson, 1980). The rate of vaporization of mercury from homogenates of liver or kidneys of animals treated with methyl mercury has been demonstrated to be proportional to the amount of inorganic mercury in these tissues. In short, it appears that inorganic mercury released into mammalian tissues by the demethylation of methyl mercury enters the oxidation-reduction cycle for inorganic mercury.

4.1.4.2 Speciation--Several different chemical and physical species of mercury are known to exist in blood following exposure to mercury vapor. These species are indicated in a general form in Figure 4-3. Hg_{d}^{++} is taken to represent the divalent species that is in the form of diffusible complexes. Hg_{nd}^{++} represents those species which are protein-bound or of high molecular weight and are in equilibrium with the diffusible form. It is also possible that there exist sites of strong binding whereby mercury is trapped. Evidence for these species of mercury varies considerably from one tissue to another.

Magos (1967) identified dissolved elemental mercury vapor both in blood from mice exposed to vapor and in samples of human blood exposed *in vitro* to vapor. Recently, Satoh et al. (1981) have confirmed Magos' *in vitro* findings. A non-diffusible protein-bound or high-molecular-weight species has also been identified. Mercury in plasma is predominantly in a non-diffusible form (Berlin and Gibson, 1963). The specific protein complex may depend upon the dose of mercury and, in one case, has been reported to be an albumin complex (Clarkson et al., 1961). However, other complexes with globulins have also been reported (Cember et al., 1968).

When salts of divalent mercury are given parenterally along with doses of sodium selenite, a complex is formed associated with protein in which mercury and selenium are present in a one-to-one atomic ratio (Burk et al., 1974). Such complexes might represent one form of trapped mercury in the blood (Burk et al., 1977).

Little is known about the chemical forms of mercury in the brain. Ashe et al. (1953), in their studies of rabbits exposed to mercury vapor, were able to distinguish between "water-soluble and -insoluble" forms of mercury in brain homogenates. These two forms of mercury probably correspond to the non-protein- and protein-bound forms of mercury reported by Cassano et al. (1966) in brain tissue from mice and rats repeatedly exposed to mercury vapor. The ratio of the protein- and non-protein-bound forms tended to remain constant in different parts of the brain at different times after exposure to mercury vapor, suggesting an equilibrium between the two forms. These investigators were unable to detect any mercury associated with lipid material in the brain.

Examination of autopsy tissue in miners exposed to mercury vapor in Yugoslavia indicated a remarkable correlation between mercury and selenium being present in a one-to-one atomic ratio over a wide range of concentrations (Kostial et al., 1975). Observations on Japanese workers who died ten years after their last exposure indicated high residual concentrations of mercury in the brain (Takahata et al., 1970). Thus, it appears that some "trapping" of mercury may occur. Small-molecular-weight complexes have not been identified in the case of mercury vapor as has been reported with methyl mercury in brain, where a glutathione complex is believed to account for about 30 percent of the total mercury (Thomas and Smith, 1979).

Little is known about the species of mercury in fetal tissues. Sapota et al. (1974) reported higher concentrations of metallothionein in fetal liver of rats than in maternal liver. They also reported that exposure of the mother to mercury vapor leads to binding of mercury to metallothionein in the fetal liver. However, no increase in metallothionein concentration was observed in maternal or fetal liver. Webb (1983) recently reviewed the role of metallothionein in mercury metabolism in pre- and postnatal development. Livers of prenatal and suckling animals contained high concentrations of metallothionein. The hepatic metallothionein of the newborn provided immediately available binding sites for mercury, binding mercury in replacement for zinc.

Studies on adult rats exposed to mercury vapor gave no evidence of increased biosynthesis of metallothionein in the liver (Cherian and Clarkson, 1976). After doses of mercuric chloride, mercury was shown to be excreted in bile, mainly in a protein-bound form and with only trace amounts of small-molecular-weight complexes (Norseth and Clarkson, 1971), suggesting that protein-bound and diffusible forms of mercury exist in liver tissue.

The kidney has an enormous capacity to accumulate divalent forms of mercury. Exposure of rats to high concentrations of mercury vapor induced metallothionein in kidney tissue that resulted in the binding of divalent mercury (Sapota et al., 1974; Cherian and Clarkson, 1976). Clarkson and Magos (1966) identified three classes of sulfhydryl groups in kidney differing in terms of their affinity for ionic mercury. The highest-affinity site corresponded to the amount of metallothionein in kidney tissue. The ability of kidney tissue to accumulate large amounts of mercury may well be related to the induction of metallothionein in this tissue.

Although small-molecular-weight forms of mercury have not been identified in renal tissue, evidence from examination of urine samples suggests that they exist. Mudge and Weiner (1958), in their study on the mechanism of action of mercurial diuretics, identified mercuric cysteine complex in urine of dogs. Other workers using sephadex column chromatography have identified a variety of molecular weight species of mercury in the urine (Piotrowski et al., 1973). These data must be considered as indirect evidence at best. Cysteine complexes in urine could originate from tissues other than kidney and might ultimately derive from the breakdown of protein complexes.

The different forms of mercury in urine are consistent with the observations of Henderson et al. (1974) on occupationally exposed workers. The authors were able to identify three distinct forms of mercury. One was elemental mercury, which could be removed by "degassing" the urine sample. A second form was released from urine by reduction with stannous chloride, and a third form could be liberated from the urine sample only after complete organic destruction. The form reducible by stannous chloride was probably the mercuric cysteine complex identified by Mudge and Weiner (1958), as this complex is known to be readily reducible by stannous chloride (Clarkson and Greenwood, 1970).

Stopford et al. (1978), studying workers exposed to 0.016-0.68 mg Hg/m^3 of mercury vapor, found that Hg^o could be detected in urine at levels less than 2 μg Hg/l. Yoshida and Yamamura (1982) confirmed these findings in thermometer workers who were exposed to air concentrations as high as 0.67 mg Hg/m^3. Elemental mercury in urine never accounted for more than one percent of total mercury in these workers. The authors suggested that Hg^o in blood is filtered at the glomerulus, thereby, explaining its rapid appearance in urine. Inorganic divalent mercury, Hg^{++}, on the other hand, is first taken up by kidney tissue before being excreted in urine. The authors concluded that Hg^{++} in urine reflects kidney levels of mercury, whereas Hg^o in urine reflects blood levels of Hg^o and, therefore, very recent exposure to the metal.

Other factors may also contribute to the variability in urinary excretion of mercury. Highly variable and fluctuating concentrations of mercury vapor may exist in the microenvironments of the workers (Henderson, 1973).

The kidney appears to play a double role with regard to mercury vapor toxicity (for review, see Magos, 1973). On the one hand, it is a target for the action of mercury (see Chapter 5). In accumulating high amounts of mercury, however, the kidney also serves as a sink, maintaining lower concentrations in other tissues and so playing a protective role in regard to these tissues. The fact that metallothionein is induced in kidney tissue (Cherian and Clarkson, 1976) further adds to the possibility of a protective role played by this organ.

4.1.4.3 Transport--Mercury vapor is a monatomic gas, highly diffusible and soluble in lipids (the heptane-to-water partition coefficient is approximately 20). These properties are believed to account for its rapid and virtually complete diffusion across the alveolar membranes in the lung (Friberg and Vostal, 1972).

The back diffusion of mercury vapor dissolved in plasma into expired air has been shown to occur in animals receiving an intravenous (i.v.) injection of a saline solution containing dissolved Hg^0 (Magos et al., 1973). Seventeen percent of the injected dose was exhaled. The observation of mercury in expired air in humans who have been exposed to mercury vapor is further evidence that the diffusion can occur from blood to expired air (Hursh et al., 1976).

The transfer of mercury from the blood to brain is believed to occur primarily by diffusion of the dissolved vapor from the plasma across the blood-brain barrier. This conclusion is based on the observation that brain concentrations of mercury are approximately ten times greater in animals exposed to mercury vapor versus those exposed to equivalent doses of ionic mercury (Berlin and Johansson, 1964). A diffusible form of mercury in plasma, other than the dissolved vapor, has not yet been identified, in part, probably because of difficulties of analysis since at least 99 percent of mercury in plasma is in a non-diffusible form.

The processes involved in the transport of mercury from mother to fetus are probably similar to those involved in the uptake into brain. However, one important difference might be that the placenta plays an active role in the regulation of transport from mother to fetus. In Figure 4-3 it is postulated that dissolved mercury vapor is a predominant species involved in the transport from maternal blood. The evidence is that the amount of mercury found in the fetus is greater in animals exposed to mercury vapor than in those given an equivalent dose of injected mercuric salts (Clarkson et al., 1972). Also, the amount retained by the placental tissues is much less in the case of exposure to mercury vapor than in animals dosed with mercuric salts. Dencker et al. (1983) have reported that treatment of the mother with ethanol will increase the amount of mercury transferred to the fetus during maternal inhalation of mercury vapor. This finding also lends support to the idea that dissolved mercury vapor is involved in maternal-fetal transport of mercury .

The placenta may interrupt the transport of divalent mercury by the presence of high-affinity binding sites. Exposure of pregnant rats to inorganic mercury results in an increase of metallothionein concentrations in the placenta. No information is available on exposure to mercury vapor.

On the assumption that mercury vapor dissolved in plasma is the primary transport species into the brain and into the fetus, Henderson et al. (1975) have proposed that the oxidation process in the red cells represents a protective mechanism. The more rapidly mercury vapor is oxidized to the divalent forms, the less it is available for transport to the brain. Henderson has proposed that as the concentration of inhaled vapor is increased, at some point, the oxidation capacity of the red blood cells will be exceeded. At this point, the dissolved mercury levels will rise rapidly in plasma with a consequent rapid transport to the brain. The "saturation" of the oxidation process might be regarded as a threshold above which effects would be expected in the central nervous system.

In support of this theory, Henderson et al. (1974) noted that workers exhibiting signs and symptoms of mercury poisoning were those that had detectable levels of elemental mercury in their urine samples. These occurred at air concentrations in excess of 0.5 mg/m^3. Below this air concentration, the authors reported no adverse effects on workers, and no detectable dissolved elemental mercury was found in the urine samples. As the concentration of total mercury increased (Figure 4-6), there was, at first, a gradual increase in elemental and reducible mercury in the urine samples, but at higher concentrations of total mercury, the concentration of these forms of mercury increased much more sharply.

To experimentally test their ideas, Henderson et al. (1975) gave the same total exposure to three groups of rats. The concentration of mercury vapor was 0.1, 0.2, and 0.6 mg Hg/m^3 and the corresponding exposure times each day were 90, 45, and 15 minutes, respectively. The mercury levels in the brain after 10 days and 19 days of exposure were 0.9 mg/m^3 for the highest vapor level, 0.5 to 0.3 mg/m^3 for the intermediate level, and 0.3 to 0.35 mg/m^3 for the lowest level. This increase in brain concentration with increased intensity of exposure for the same total exposure supports the concept that a rapid rate of entry of vapor into the bloodstream tends to overwhelm the oxidative capacity of the red cells.

Loss of mercury from the brain has been observed in humans and animals after exposure to mercury vapor (as discussed above). Hg^0 would be one possible transport species in view of its high diffusibility and lipid solubility. Shortly after exposure, vapor already deposited in the brain may diffuse outward as the blood concentration of Hg^0 falls. At later times, the mobilization from brain tissue to blood might be, in part, mediated by a reduction process occurring in the central nervous system. To what extent this reduction process plays a role in the movement of diffusible complexes of divalent mercury is not known. Thus, critical information is lacking as to the pathways by which mercury is removed from the brain after exposure to mercury vapor.

This reduction process raises the possibility that the mobility of inorganic mercury in the body might be mediated by the atomic species. It is also possible that diffusible forms of divalent mercury play a role in transport.

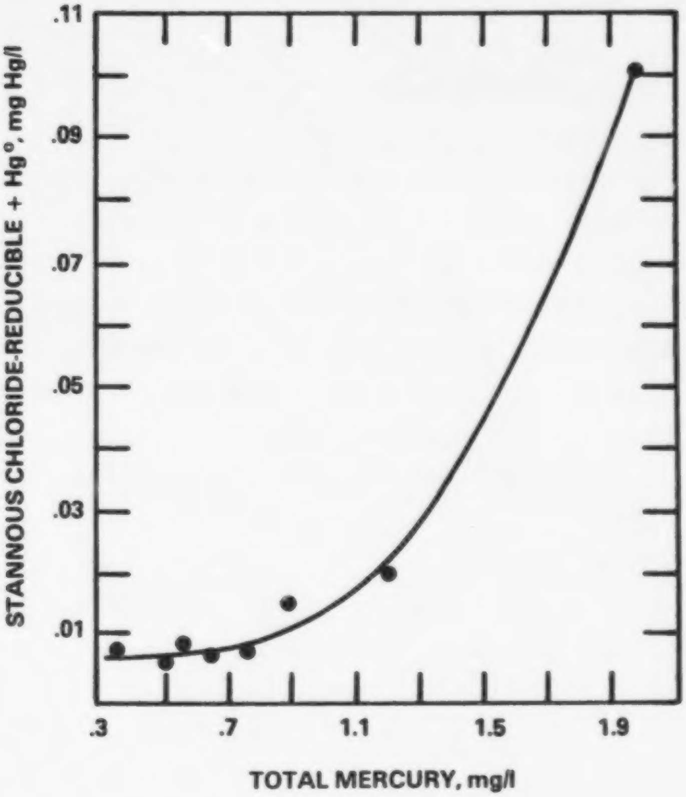

Figure 4-6. Group averages of total mercury versus stannous chloride-reducible mercury plus elemental mercury in urine.

Source: Henderson et al. (1974).

For example, Doherty (1977) noted a rapid transport of mercury into the fetus immediately after exposure to the vapor. Animals given the equivalent dose of the ionic salt exhibited a slower movement of mercury to the fetus; however, after 24 hours, the fetal levels were similar in both groups. Thus, it is important to look into the question of repetitive exposures to mercury vapor. The possibility exists that, as the burden of the oxidized form of mercury accumulates, a diffusible species of divalent mercury might play an increasing part in transport to the fetus.

4.2 COMPOUNDS OF INORGANIC MERCURY

4.2.1 Compounds of Mercurous Mercury

Very few quantitative data are available on the pharmacokinetics of compounds of mercurous mercury. Calomel was widely used in teething powders for children and as a vermifuge until about 1951, when it was discovered to be the cause of the childhood disease of "Acrodynia" (Warkany and Hubbard, 1948). Calomel is highly insoluble in water; thus, it was assumed to be poorly absorbed from the gastrointestinal tract. Some absorption must occur, however, as very high tissue levels have been reported (527 µg Hg/g in the kidney) in at least one individual who took calomel as a laxative over a long period (Weiss et al., 1973).

The intravenous administration of mercurous mercury (Hg_2^{++}), as calomel, to laboratory animals (rats, rabbits, and guinea pigs) resulted in the deposition of mercuric ions in kidney and red blood cells, as evidenced by histochemical methods (Hand et al., 1944). An autopsy report of an individual who had chronically ingested calomel indicated the presence of mercuric sulfide crystals in cells in kidney, liver, and intestinal tissues (Weiss et al., 1973). The mechanism of conversion of mercurous to mercuric mercury in mammalian tissues is unknown. It may result from the disproportionation of the mercurous ion known to occur in vitro in the presence of -SH groups, i.e.:

$$Hg_2^{++} \longrightarrow Hg^{o} + Hg^{++}$$

4.2.2 Compounds of Mercuric Mercury

Quantitative data on pulmonary retention of compounds of mercuric mercury are lacking in humans. Mercuric oxide aerosol (mean diameter, 0.16 µm) was retained in the dog (Morrow et al., 1964). Approximately 45 percent of the aerosol was cleared in 24 hours; the remainder had a half-time of 33 days.

Approximately 15 percent of a tracer dose of mercuric nitrate (6 μg Hg/adult) given orally as an aqueous solution or attached to liver protein was absorbed from the gastrointestinal tracts of adult volunteers. Animal data confirm that gastrointestinal absorption is 15 percent or less (for review, see Clarkson, 1972). Gastrointestinal absorption in suckling animals is much higher, on the order of 50 percent of an oral dose (Kostial et al., 1978).

Inorganic mercury is absorbed across the skin, but quantitative data are lacking in humans. Friberg et al. (1961) found that 8 percent of mercuric chloride applied to the skin of experimental animals was absorbed within five hours.

Mercuric mercury is transported in the bloodstream, being present in roughly equal concentrations in plasma and red blood cells (for a recent review, see Berlin, 1983). In plasma, it is protein bound, the distribution between different proteins depending upon dose, time, and method of administration.

Mercuric mercury penetrates, to a small degree, the blood-brain and the placental barriers. Deposition in various tissues and organs shows great differences and is dependent on time, dose, and route of administration. Data on steady-state tissue levels are lacking for both man and animals. After a single dose, the kidney is the main site of deposition; according to studies in several animal species, approximately 30 percent of the dose is initially deposited in the kidney. Approximately two weeks after a single dose to rats, as much as 90 percent of the remaining body burden is located in the kidneys (Rothstein and Hayes, 1960). Concentrations of inorganic mercury in other tissues are much lower, as already described for inhaled mercury vapor. Autoradiographic observations on mice, given a single non-toxic dose of Hg^{++}, indicate that localized accumulation also occurs in the cells of mucous membranes in the intestines, the epithelial layers of the skin, the spleen, the interstitial cells of the testicles, and the choroid plexus in the brain (Berlin and Ullberg, 1963a).

The urinary and gastrointestinal tracts are the principal pathways of excretion. In a study by Rahola et al. (1973), it was noted that fifty days after a single oral dose of mercuric mercury, urinary and fecal excretion were of approximately equal magnitude in ten adult volunteers. The pathways involved in fecal excretion are not known in detail, but inorganic mercury is known to be secreted in saliva and bile, and by cells of the large intestine. Urinary excretion probably occurs via the uptake of mercury from plasma to renal tubular cells and subsequent release into the tubular fluid (for review, see Berlin, 1983). Excretion probably also occurs in sweat, and a small amount may be excreted in expired air as noted in observations on people exposed to mercury vapor (see Section 4.1).

The biological half-time in the whole body was found to be 42 days (SE = 3 days) in ten volunteers receiving a single oral tracer dose of inorganic mercury compounds (Rahola et al., 1973). Five females in the group had an average half-time of 37 ± 3 days and five males had an average half-time of 48 ± 5 days. The biological half-time in the red blood cells for the whole group was 28 ± 6 days, significantly lower than the whole body. The biological half-time in plasma of a 17-year old girl who had received a toxic dose of inorganic mercury was also in the range reported by Rahola and co-workers for red blood cells (Newton et al., 1983).

4.3 METHYL MERCURY COMPOUNDS

Observations on volunteers have indicated that approximately 95 percent of an oral dose of methyl mercury is absorbed in the gastrointestinal tract regardless of whether the methyl mercury is given as a simple salt (methyl mercury nitrate) (Aberg et al., 1969), is attached to liver protein, (Miettinen, 1973), or is naturally present in oceanic fish, such as tuna (Turner et al., 1975). Observations on individuals who accidentally consumed toxic amounts of methyl mercury fungicide in homemade bread suggest that absorption is virtually complete (Al-Shahristani et al., 1976).

Methyl mercury distributes much more uniformly throughout all the tissues of the body as compared to inorganic mercury. Observations on volunteers given a single radioactive dose of methyl mercury have indicated that most of the tissue distribution is complete within a few days (Aberg et al., 1969; Miettinen, 1973). When distribution was completed in these volunteers, approximately 10 percent of the radioactivity was found in the head region, presumably in the brain, and approximately 7 percent was found in the blood compartment. The figure for the blood compartment was confirmed by observations on volunteers ingesting a measured dose of methyl mercury in fish (Kershaw et al., 1980).

As a consequence of the mobility of methyl mercury in the body, tissue concentration ratios tend to be constant. For example, the plasma-to-red blood cell concentration ratio in man is approximately 10:1 according to observations on volunteers (Miettinen, 1973; Kershaw et al., 1980) and on individuals who ingested toxic doses of methyl mercury (Bakir et al., 1973). The blood-to-brain ratio has been shown to be approximately constant within species, and, therefore, blood may be used as an index of average concentrations in the brain (the target tissue) (Nordberg, 1976). Observations on volunteers taking radioactive methyl mercury (Aberg et al., 1969) and on non-human primates (Berlin et al., 1975; Evans et al., 1977; Willes et al., 1978) indicate that the blood-to-brain ratio is approximately 5.

Methyl mercury readily crosses the placenta. Observations on fish eaters in Sweden have indicated that fetal blood is about 20 percent higher than maternal blood (Swedish Expert Group, 1971), but, in an Iraqi outbreak, ratios much higher than this were reported in mothers receiving toxic doses of methyl mercury in bread (Amin-Zaki et al., 1974; 1976).

Methyl mercury accumulates in hair at the time hair is formed in the follicle. Once incorporated into hair, the mercury concentration does not change. Since hair grows approximately one centimeter a month, each centimeter segment of hair represents one month's average blood concentration for that month during which the hair was formed.

Hair-to-blood concentration ratios have been measured both in volunteers ingesting a measured dose of methyl mercury, as well as in individuals exposed to methyl mercury from fish in their diet and in people who accidentally received toxic doses of methyl mercury as occurred in Japan and Iraq. Since there is individual variation in the hair-to-blood concentration ratios (Phelps et al., 1980), it is preferable, when collecting hair samples, to obtain at least one blood sample to determine the ratio for that particular individual.

Methyl mercury is slowly broken down to inorganic mercury in mammals. The fraction of total mercury present in tissues as inorganic mercury depends on the duration of exposure to methyl mercury and the time after cessation of exposure. The kidneys usually contain the highest fraction of inorganic mercury; values as high as 70 percent were reported approximately two months after a single dose of methyl mercury was administered to rats (Norseth and Clarkson, 1970). In this same study, the percentage of inorganic mercury in the central nervous system of rats was low, never exceeding 4 percent.

The percentage of inorganic mercury in human tissues in samples collected about two months after the end of exposure in the above mentioned Iraqi outbreak has been reported by Bakir et al. (1973), Magos et al. (1976), and Amin-Zaki et al. (1976). The following fractions (expressed as percentage total mercury) were found in human tissues and fluids: whole blood, 7 percent; plasma, 22 percent; milk, 39 percent; liver, 16 to 40 percent; and urine, 73 percent. Inorganic mercury accounted for about 5 percent of total mercury in whole blood and about 20 percent in samples of head hair taken from a population consuming methyl mercury in fish (Phelps et al., 1980).

The fecal pathway accounts for most of the excretion of total mercury in animals (Norseth and Clarkson, 1970), and inorganic mercury accounts for virtually all the mercury in human feces (Turner et al., 1975). Urinary mercury accounts for less than one-third of total excretion, and hair and milk do not contribute significantly to total excretion. Thus, the elimination of mercury from the body of humans after exposure to methyl mercury depends almost entirely on conversion to inorganic mercury.

The site of conversion of methyl to inorganic mercury in the body has not yet been identified, but there is evidence that the intestinal flora may be involved in the breakdown of methyl mercury (Rowland et al., 1980; Nakamura et al., 1977). Methyl mercury is secreted in bile of rats (Norseth and Clarkson, 1971) and non-human primates (Berlin et al., 1975), but it is reabsorbed back into the bloodstream. Only conversion to inorganic mercury prevents this reabsorption. Evidence for secretion of methyl mercury in bile in human subjects is mainly indirect. A thiolated resin known to trap methyl mercury secreted in bile in animals and to prevent its reabsorption has been shown to be effective in increasing fecal excretion in human subjects (Clarkson et al., 1979).

Observations on volunteers taking a tracer dose of radioactive methyl mercury indicate that the body burden of radioactivity declines according to first order kinetics and, therefore, can be characterized by a single biological half-time (Aberg et al., 1969; Miettinen, 1973). The biological half-time in adult males is 79 days and in adult females is 71 days. The half-time in blood in the same series of studies was found to be, on the average, 50 days, with a standard deviation of 7 days. The biological half-time was found to be 52 days in five volunteers ingesting a measured amount of methyl mercury in fish (Kershaw et al., 1980). A half-time of 65 days was reported for 16 patients who were heavily exposed in Iraq (Bakir et al., 1973). Al-Shahristani and Shibab (1974) used hair samples to calculate biological half-times of methyl mercury in the victims of the Iraqi outbreak. These authors calculated the biological half-time in the blood compartment from the rate of decline in concentration along the length of a hair sample after exposure had stopped. The length along the hair was converted to time from the measured growth of the hair strands. They found an average biological half-time in hair of 72 days, but half-times had a very wide range (35 days to 189 days). This wide range of biological half-times may have been due, in part, to errors in hair analysis and to uncertainties in hair growth (Giovanoli-Jakubczak and Berg, 1974). Nevertheless, the mean value of 72 days was close to the 65-day value observed by direct blood analysis in the Iraqi victims. A wide range of biological half-times in blood or in red blood cells has also been observed in a few individuals who have consumed methyl mercury in fish (Birke et al., 1972).

Biological half-times have been reported for radioactivity in the head region in three volunteers who ingested a single tracer dose of radioactive methyl mercury (Aberg et al., 1969). The reported biological half-times for the head region did not differ significantly from those reported for the whole body. However, Japanese investigators, analyzing samples of brain tissue several years after what was believed to be cessation of exposure to methyl mercury, estimated that half-time in the brain could be more than 200 days (Takeuchi and Eto, 1975). Unfortunately, it is not clear whether or not ingestion of methyl mercury had, indeed, ceased in the study individuals. Observations on a deceased individual in Northwestern Quebec, who had blood levels as high as 600 ng/ml two years prior to death, indicated that brain levels at the time of death were virtually normal. If correct, this finding would dispute a biological half-time of 200 days in brain tissue (Wheatley et al., 1979).

The biological half-time of methyl mercury in suckling infants is not known, but observations in rodents indicate that mercury is not eliminated from the body when methyl mercury is given during the suckling period (Doherty, 1977).

From the above information, it can be surmised that the accumulation and excretion of methyl mercury in man can be represented by a simple one compartment model. Roughly 95 percent of an oral dose is absorbed into the body, and, on the average, about 1 percent of this amount (equivalent to a biological half-time of 69 days) is eliminated per day. Equations describing the accumulation of methyl mercury in the whole body, in the blood compartment, and in hair have been presented elsewhere (World Health Organization, 1976; Environmental Protection Agency, 1980, 1984). These equations have been used to characterize the accumulation of mercury, assuming an individual receives a constant average daily intake until a steady state is reached, followed by an elimination phase where intake is stopped. In general, it takes approximately 5 biological half-times to attain steady state, i.e., where intake balances excretion. With a biological half-time in the whole body of approximately 70 days and a biological half-time in blood (and, therefore, hair) of approximately 50 days, it would take roughly one year to attain a state of balance. Likewise, upon cessation of exposure, it would take another year for the amount in the tissue compartments to fall to pre-exposure levels.

4.4 PHENYLMERCURY AND RELATED COMPOUNDS

In the last decade, a number of general reviews on mercury have included the pharmacokinetics and metabolism of phenylmercury compounds (World Health Organization, 1976; Nordberg, 1976; Environmental Protection Agency, 1980). Phenylmercury compounds are usually assumed to be toxicologically representative of other aryl and alkoxyaryl mercurials (Goldwater, 1973). This assumption is somewhat tenuous as most of the available data are restricted to phenylmercury compounds. Furthermore, most of what is known about phenylmercury compounds comes from experimental animal studies despite the fact that human exposure to such compounds is not uncommon.

Phenylmercury is rapidly metabolized to inorganic mercury. Following a single dose of phenylmercury, the absorption, transport, and initial tissue distribution of mercury is similar in some respects to that of other organic mercurials such as methyl mercury. Within one week, tissue distribution and excretion approximates that seen after doses of inorganic mercury compounds.

Studies on exposed populations suggest, but do not prove, that phenylmercury compounds can be absorbed across the skin (Goldwater, 1973). Several thousand infants exposed to a phenylmercury fungicide in their diapers had urine levels substantially higher than non-exposed infants (Gotelli, 1982).

Laug and Kunze (1949) demonstrated that, in rats, phenylmercury compounds were well absorbed from the vaginal tract -- approximately 75 percent of the administered amount in about 8 hours. In addition, women using phenylmercury spermicidal preparations were reported to have small elevations in urinary mercury concentrations (Eastman and Scott, 1944).

The efficiency of absorption of oral doses is not known in humans. Experiments on mice indicate that gastrointestinal absorption is greater than 80 percent of the dietary intake (Clarkson, 1971). Experiments on a variety of animal species indicate that gastrointestinal absorption of phenylmercury compounds is much greater than compounds of inorganic mercury (Ellis and Fang, 1967; Fitzhugh et al., 1950; Miller et al., 1967; Roberts et al., 1979).

Phenylmercury appears to be reabsorbed intact into the blood stream, where it tends to distribute to a greater extent into the red cells than into plasma (Miller et al., 1960; Gage, 1964; Berlin, 1963). Phenylmercury distributes rapidly from the bloodstream to soft tissue, the highest concentration of the intact mercurial being found in the liver. Transport across the blood-brain and placental barriers appears to be minimal, much less than methyl mercury and similar to inorganic mercury (Yamaguchi and Nunotani, 1974; Berlin and Ullberg, 1963b).

The intact mercurial disappears from body tissues within a few days due, in part, to excretion, but mainly due to metabolic transformation to inorganic mercury (Miller et al., 1960; Gage, 1964; Ellis and Fang, 1967). The metabolic conversion is believed to involve hydroxylation of the benzene ring, resulting in an unstable metabolite that spontaneously releases inorganic mercury (Gage, 1973). The released inorganic mercury then rapidly accumulates in the kidney. Generally, within one or two weeks after cessation of exposure, the pattern of distribution approximates that of inorganic mercury.

Fecal excretion is the dominant pathway of excretion in the first few days after dosing. This may be related to biliary excretion and to the pronounced accumulation in epithelial cells of the gastrointestinal tract (Berlin and Ullberg, 1963b). In the first day or two, urinary mercury is mainly in the form of the intact mercurial. This condition is followed by a delayed excretion of inorganic mercury which, in rats, has been shown to reach a maximum in approximately four days (Gage, 1964). Urine samples taken from infants chronically exposed to phenylmercury acetate in their diapers contained mainly, if not entirely, inorganic mercury (Gotelli, 1982).

Some accumulation of mercury in rat fur has been found after repeated dosing of phenylmercury; however, the reported concentrations were about ten times lower than those observed after similar dosing with methyl mercury (Gage, 1964).

4.5 SUMMARY

The pharmacokinetics and biotransformation of mercury depends upon its chemical and physical form.

In the case of mercury vapor, approximately 80 percent of inhaled vapor is absorbed across the lung and retained in the body. Mercury distributes via the bloodstream to all tissues in the body, the initial distribution process being complete in about three days. Within the blood, concentrations in red cells tend to be higher than in plasma shortly after exposure to mercury vapor. Mercury readily penetrates the blood-brain and placental barriers after exposure; however, the kidney is the major site of accumulation. Mercury is predominantly excreted in urine and feces at approximately equal rates.

The half-times of mercury vary within the body. The whole body half-time is approximately 50 days whereas the half-time in the brain is about 20 days. The blood contains two compartments having half-times of about 3 and 30 days each. Blood levels can serve as indicators of recent mercury vapor exposure. Conversely, urine levels correlate with long-term exposure, however, only on a group basis. Individual variability of urine levels can be considerable.

Inhaled mercury vapor is oxidized to divalent ionic mercury in body tissues by the hydrogen-peroxide catalase pathway. This oxidation step is inhibited by non-intoxicating doses of ethanol. Pretreatment with ethanol can lead to decreased retention and increased exhalation in the lung. Dissolved mercury vapor in plasma is believed to be the species transported to the brain and the fetus and may be important in transport and distribution to all tissues in the body. Inhalation of mercury vapor can lead to the induction and binding of mercury to metallothionein in the kidneys. After long-term (lifetime) exposures, mercury has been reported to exist in tissue bound, at least in part, to selenium in a 1 to 1 atomic ratio.

In the case of inorganic divalent mercury, approximately 15 percent of an oral, non-toxic dose is absorbed from the gastrointestinal tract in adults and retained in body tissues. In children, the gastrointestinal absorption is probably greater. The kidney is the predominant site of inorganic mercury accumulation, but accumulation also occurs in the cells of the mucous membranes of the gastrointestinal tract. This form of mercury penetrates the blood-brain and placental barriers only to a small extent. Excretion is mainly via urine and feces at roughly equal rates by each pathway. The whole body half-time in adults is about 40 days. Inorganic divalent mercury can induce and bind to metallothionein in the kidney and probably forms complexes with selenium in tissues after chronic exposure.

Methyl mercury compounds are absorbed almost completely in the gastrointestinal tract and retained in the body. Certain methyl mercury compounds are probably well absorbed across the skin. Distribution takes place via the bloodstream to all tissues in the body, the initial phase being complete in about three days. The pattern of tissue distribution is much more uniform than after inorganic mercury exposure except in red cells where the concentration is ten to twenty times greater than the concentration in plasma. Methyl mercury readily crosses the blood-brain and placental barriers, and as with other forms, the kidneys retain the highest tissue concentration.

At the end of the initial phase of distribution, approximately one percent of methyl mercury is found in one liter of blood in the 70-kg human adult. The brain-to-blood concentration ratio is about 5:1. Methyl mercury accumulates in hair in the process of formation of hair strands. The hair-to-blood concentration ratio is approximately 250:1 in humans. Once incorporated into the hair, this concentration remains unchanged. Excretion is predominantly via the feces. Methyl mercury is slowly broken down to inorganic mercury and most, if not all, of the excreted mercury is in the inorganic form. Animal experiments indicate that fecal excretion originates, at least in part, from biliary secretion.

The whole body half-time of methyl mercury is usually between 70 to 80 days, but substantial individual differences occur. The brain half-time is roughly the same as the whole body, whereas the half-time in the blood compartment is about 50 days. Blood concentration is a useful indicator of body burden, and hair concentration, when measured along the length of a hair strand, is a useful indicator of past blood levels.

Phenylmercury compounds are well absorbed across the intestinal tract and retained by the body. They are probably absorbed across the skin as well. They are carried in the bloodstream and deposited in most tissues, but penetration to the brain and to the fetus is much less than is the case with methyl mercury compounds. In this regard, phenylmercury compounds are much more similar to inorganic mercury compounds. The kidney is, again, the predominant site of accumulation, and excretion is via urine and feces. Most of the distribution and excretion patterns can be understood by the fact that phenylmercury compounds are rapidly broken down to inorganic mercury. The intact mercurial is usually not detectable in animal tissue one week after exposure has stopped.

5. TOXIC EFFECTS OF MERCURY IN MAN AND ANIMALS

5.1 VAPOR OF METALLIC MERCURY

5.1.1 Local Effects

Acute exposure to high concentrations of mercury vapor may lead to metal fume fever and pneumonitis. Garnier et al. (1981) reported on two cases of acute mercury vapor exposure and reviewed the literature on twenty other cases (also, see Milne et al., 1970). Ten percent of the fatalities which occurred in the cases were due to lung damage. In most cases, an acute gingio-stomatis was generally observed, but encephalopathy and renal damage were uncommon.

In a recent review of the literature, Jaffe et al. (1983) noted that infants 4 to 30 months of age appear to be more susceptible than older children and adults to the direct effects of mercury vapor. In case reports, acute exposure to mercury vapor was shown to cause exudative alveolar and intestinal edema and erosion, necrosis and desquamation of the bronchiolar epithelium. Actual vapor concentrations were not measured, but the nature of these acute exposures suggests that the vapor concentrations were very high. The reason for the increased susceptibility of infants is not known, but it may be due to the increased exposures experienced by the infants as they crawl on the floor where mercury vapor concentrations would be highest.

Contact dermatitis may result from exposure to liquid metallic mercury when prolonged skin contact occurs (Hunter, 1969). This manifests itself as a papular erythema with slight hyperkeratosis. It should be noted, however, that this particular effect of metallic mercury has not been widely reported in the literature.

5.1.2. Systemic Effects

The major systemic effects of inhaled mercury have been described since antiquity (for reviews, see Ramazzini, 1713; Hunter, 1969; Goldwater, 1972). These major effects classically present as erethism, tremor and gingivitis. More recently, Trachtenberg (1969) and Smith et al. (1970) have described a milder form of poisoning involving a number of non-specific neurological and psychological symptoms. The signs and symptoms of systemic mercury vapor poisoning are described in more detail below, classified according to the function or tissue that is affected.

5.1.2.1 Behavioral and Neurological Effects--The major behavioral effects in man are usually described by the term erethism. This syndrome includes a number of psychological effects: excessive introversion, emotional lability, irritability and anxiety. Hallucinations, delusions, and mania have been noted in the severe forms of erethism. In previous centuries, mercury was used in the manufacture of mirrors, and erethism was a common effect in the mirror makers of Venice (Ramazzini, 1713) and Furth and Nürnberg (Kussmaul, 1861). Hunter (1969) has noted that erethism is now rare. Milder, less obvious and less specific behavioral changes have been reported in occupational exposures to levels of mercury that are lower than those thought to lead to fully developed erethism. For example, Smith et al. (1970) found that an increase in complaints of insomnia, loss of appetite, weight loss and shyness were the earliest changes associated with occupational exposure to mercury vapor. Williamson et al. (1982) reported deficits in short-term memory in a group of twelve workers. All twelve were probably exposed to mercury vapor, but eight may have had additional exposure to mercuric chloride and methoxyethyl-mercury compounds. The mercury-exposed group also exhibited poor psychomotor coordination and premature fatigue as compared to a matched control group. The range of urinary mercury concentrations in the exposed group at the time of the study was from < 10 to 670 μg Hg/l with a mean value of approximately 132 μg Hg/l. Urinary mercury values measured over the five previous years were in the same range. However, it should be noted that some workers that had current low values had much higher urine levels at earlier examinations. The work of Langolf et al. (1978) indicates that exposures which induce short-term memory deficits occur at levels lower than those that cause damage in psychomotor function.

The association between mercury vapor exposure and emotional disturbances has been the subject of some controversy. Chaffin et al. (1973) consider emotional disturbances to be a consequence of psychomotor disturbances, whereas Vroom and Greer (1972) consider them as secondary to memory deficits.

Forzi and co-workers (as cited by Hanninen, 1982) conducted two studies on mercury workers. The first study found that neurotic and introvert personality traits were associated with exposure to mercury vapor, but the second follow-up study found only neuroticism associated with such exposure. Angotzi et al. (1980), using the personality inventory of Cattell, noted a tendency towards anxiety and introversion in mercury-exposed workers.

Shapiro et al. (1982) have reported that disturbances in neurophysiological and neuropsychological function occur at low tissue levels common in the dental profession. In a group of dentists exposed to high levels of mercury (as determined by analysis of dentine in teeth; N = 24), 30 percent had polyneuropathies as compared to zero percent in the controls ($P < 0.01$). Mild neuropsychological effects were indicated by higher distress values, as recorded on a self-reporting check list ($P < 0.05$), and lower scores on the Bender-Gestalt test ($P < 0.01$).

Neurological effects mainly present in the form of an intention tremor. Hunter (1969) noted that mercurial tremor, though seldom the first sign to appear, is the most characteristic sign of neurological disorder. It is not as fine or as regular as tremor due to hyperthyroidism, and it is interrupted every few minutes by coarse, jerky movements. In a more recent study, Wood et al. (1973) presented tracings that were recorded from a patient suffering from occupational mercury vapor poisoning and compared them to tracings recorded after the patient had recovered (Figure 5-1). Chaffin et al. (1973) and Langolf et al. (1978) also measured tremor in chlor-alkali workers exposed to mercury vapor. Chaffin et al. (1973) reported a statistically significant correlation between mean tremor frequency and current urinary mercury concentrations. The scatter of the individual data points was so great it was not possible to identify a lower effect level. Both Chaffin's and Langolf's groups noted that shifts in the power spectrum were correlated with elevated urinary mercury concentrations.

In summary, recent studies have added information to that found in the landmark papers of Neal et al. (1941) and Smith et al. (1970), indicating that motor system disturbances may be more reversible than decrements in cognitive functions (mainly memory deficits). It can be surmised from these studies that introversion appears to be the most prominent personality trait. The fact that motor changes are more easily detected and more likely to be reversed upon exposure cessation suggests, as stated by Hanninen (1982), that "the more insidiously developing cognitive decrements and emotional alterations may be the most harmful health hazard for mercury workers today."

A number of case reports and studies of occupationally exposed groups indicate that the peripheral nervous system is also affected by mercury vapor. Shapiro et al. (1982) found a high prevalence of polyneuropathies in dentists exposed to mercury vapor. Case reports by Iyer et al. (1976), Goldstein et al. (1975) and Hryhorczuk et al. (1982) provide evidence of sensory polyneuropathies. Vroom and Greer (1972), in detailed neurological studies of patients

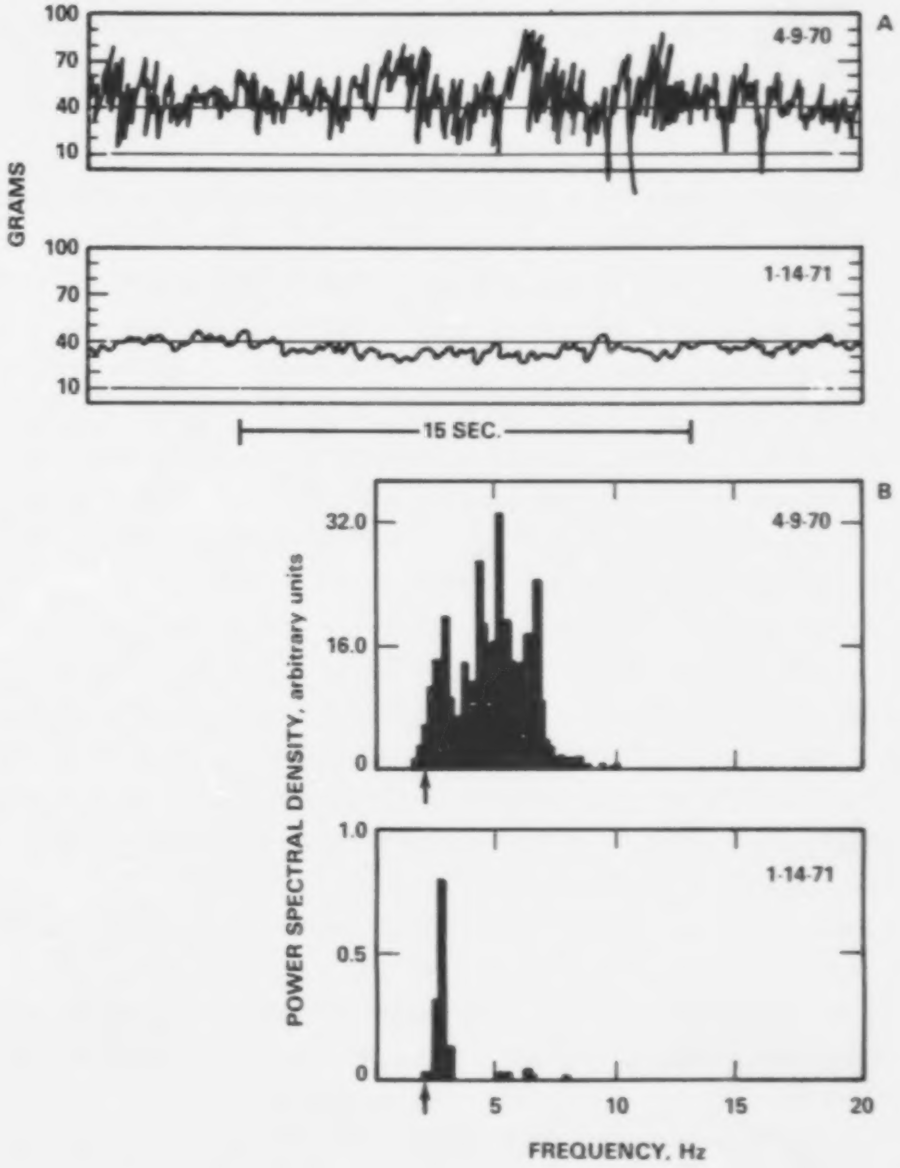

Figure 5-1. (A) Tremor tracings from a woman exposed to mercury vapor in a plant using metallic mercury to calibrate pipets. The upper tracing was recorded when the victim first was seen at the hospital. The lower tracing was recorded 9 months later, with no intervening exposure. Recordings were made by having the patient rest the index finger in a Lucite slot attached to a strain gauge while attempting to maintain a force between 10 and 40 g. (B) Tremor spectra corresponding to the tracings in (A). Strain gauge output was amplified and fed to the analogdigital convecter of a PDP-12 computer. The power spectrum was calculated by a Fast Fourier Transform. Note the multiple peaks in the spectrum corresponding to the more severe tremor.

Source: Wood et al. (1973).

suffering from mercurialism, found that one patient had limb weakness, another had distal paresthesias, and two had fasciculations and cramps. The authors suggested that damage to the anterior horn cells and axonal degeneration would explain most of these abnormalities. This suggestion was supported by electromyographic observations indicating involvement of the motor nerves reminiscent of the syndrome of amyotrophic lateral sclerosis. More recently, Levine et al. (1982) performed nerve conduction tests on eighteen workers exposed to mercury vapor in a chlor-alkali plant. Average urinary mercury concentrations ranged from 20 to 450 µg/l with a group mean (spot samples) of 290 µg/l over a three-year observation period. The authors found that prolonged motor and sensory distal latencies correlated with increasing urine mercury concentrations as integrated over the time of the study.

In a case report on a 54-year old man who experienced a two-day exposure to high levels of mercury vapor, (the air concentration must have been very high as it resulted in a urine concentration of 100 µg Hg/l), Adams et al. (1983) noted that the man developed a syndrome resembling amyotrophic lateral sclerosis. The syndrome disappeared when urinary mercury returned to normal. The authors speculated that mercury toxicity must be considered "not only in individuals with recent anterior horn-cell dysfunction, but also with otherwise unexplained peripheral neuropathy, tremor, ataxia, and a gamut of psychiatric symptoms, including confusion and depression".

Animal studies have attempted to reproduce the neurological and behavioral effects of inhaled mercury vapor. Armstrong et al. (1963) were the first to report behavioral effects in animals. At very high mercury concentrations (17 mg Hg/m^3, i.e., a virtually saturated atmosphere), a decrement in performance was noted in pigeons trained to certain pecking routines. Subsequently, Beliles et al. (1968) also found decrements in the conditioned behavior of rats exposed for 15 days to the same mercury concentration (17 mg Hg/m^3). Fukuda (1971) was able to elicit a "fine" tremor in the fore and hind limbs of two of six rabbits exposed intermittently to mercury vapor (average concentration of 4.0 mg Hg/m^3 for 6 hr/day, 4 days/week, for 13 weeks). The brain concentrations ranged from 0.8 to 3.7 µg Hg/g wet tissue. Kishi et al. (1978) found a decline in conditioned avoidance response in rats after exposure to 3 mg Hg/m^3 for 3 hr/day, 5 days/ week. The time to onset of effects varied from 12 to 39 weeks. All rats recovered to pre-exposure baseline levels of performance within 12 weeks after the termination of exposure. Significantly poor performance was noted at brain concentrations of 20 μg Hg/g wet weight and recovery to normal behavior was observed when the brain levels fell to 10 μg Hg/g wet weight. No pathological changes in brain tissue were observed.

Unfortunately, animal experiments have so far failed to find an appropriate animal model for man. The signs observed in animals are not obviously related to effects in humans, and very high concentrations are needed to produce behavioral and neurological effects.

5.1.2.2 Oral Effects--Salivation and tenderness of the gums and mouth are usually early symptoms of mercury vapor poisoning (Hunter, 1969). The gums become swollen and readily bleed. Occasionally, a mercurial line is visible on the gums. It usually resembles the blue line caused by lead exposure. Early loss of teeth may result from occupational exposure to mercury vapor. In historical accounts of mercury poisonings, Kussmaul (1861) noted that in the towns of Furth and Nürnberg, well known for their mirror-making industries, almost every adult male was without a single tooth. Such severe effects may be a legacy of the past, however, as Smith et al. (1970) did not report oral effects in their more recent study of occupationally exposed workers.

5.1.2.3 Renal Effects--Friberg et al. (1953) reported two cases of nephrosis in workers exposed to mercury vapor in the chlor-alkali industry. This illness, characterized by fatigue, irritability, edema of the face and ankles and the presence of protein (albumin) and hyaline casts in the urine, abated in the two reported cases within a few months upon termination of exposure. Kazantzis et al. (1962) also reported albuminuria in four workers exposed to mercury vapor and other forms of mercury. The authors noted that urine levels were in excess of 1000 μg/l, but that many workers had levels in excess of this value without exhibiting albuminuria. In one factory, two cases of albuminuria were observed, but 50 other workers similarly exposed did not develop albuminuria even though 13 of these workers had urine values in excess of 1000 μg/l. Kazantzis et al. (1962) therefore suggested that the nephrosis in these cases might have been an idiosyncratic reaction.

Smith and Wells (1960) carried out electrophoretic separation of urinary protein in workers with proteinuria due to exposure to mercury vapor. Analysis by ultracentrifugation on amino acid composition suggested the proteins originated from the serum.

Stewart et al. (1977) reported a mild proteinuria (median value: 117 mg/24 hr) in 21 laboratory technicians exposed to mercury vapor (median urinary mercury excretion: 53 μg/24 hr) as compared to a non-exposed control group (urinary proteins; 48 mg/24 hr, urinary mercury; 15 μg/24 hr). The maximum air concentration of mercury ranged up to 0.1 mg Hg/m^3.

Buchet et al. (1980) measured the urinary excretion of a number of specific proteins in a group of 63 workers from two chlor-alkali plants and in 88 control workers without occupational exposure to mercury. Values of urinary proteins were considered abnormal if they exceeded the arithmetic mean plus two standard deviations as calculated in the control group. The prevalence of abnormal values did not seem to be well correlated with mercury concentrations in blood, but the prevalence of abnormal values for high-molecular-weight proteins (albumin, transferrin) increased with increasing urinary excretion of mercury. Urinary excretion of low-molecular-weight proteins (e.g., β_2-microglobulin) was not affected.

In a subsequent study, Roels et al. (1982) were able to confirm an increased prevalence of albuminuria in 51 male workers exposed to mercury vapor when compared to a control group (51) matched for age, sex, socioeconomic status and job characteristics. The median (range) mercury levels in urine for controls were 1.3 (0.6-4.7) and for exposed were 71 (9.9-286) μg Hg/g creatinine.* Observations on psychomotor performance indicated that decrement in performance was found in mercury-exposed workers but occurred independently from the presence of proteinuria.

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*The urinary excretion of mercury is frequently expressed in this way when "spot" urine samples have been analyzed. The rate of urinary excretion of creatinine is proportional to the lean body mass, and therefore does not change greatly for a given individual or for groups of workers having roughly similar body weights. Conversely, urine volume flow rates vary greatly, depending upon the degree of hydration of the individual. The concentration of mercury in spot urine samples may be greatly affected by the degree of hydration of the subject and, therefore, not accurately indicative of the true excretion rate. Human adults excrete approximately 1 to 2 grams of creatinine per day. Therefore, expressing the mercury excretion per gram creatinine gives a rough indication of daily excretion rate and avoids errors due to fluctuations in dilution of the spot urine sample. Since normally hydrated individuals excrete between 1 and 2 liters of urine per day, the mercury excretion in μg Hg/g creatinine is approximately equal to 1 μg Hg/l urine. Expressing mercury excretion by this "creatinine correction" also has another advantage. Since creatinine excretion is proportional to lean body mass, urinary creatinine excretion is a "sizing factor." Thus, urinary mercury expressed as μg Hg/g creatinine amounts to a (lean) body weight corrected excretion rate.

Stonard et al. (1983) studied the excretion of specific proteins and enzymes in urine samples of 87 control workers (mean urinary mercury in the range of 3.3 to 4.6 µg Hg/g creatinine, based upon three separate visits) and in 105 exposed workers (mean urinary mercury in the range of 63 to 71 µg Hg/g creatinine, based upon three separate visits). The range of individual values was 0.4 to 275 µg Hg/g creatinine. The corresponding mean blood mercury values were 5 and 17.5 µg Hg/l, respectively. Highly significant correlations were found between blood and urinary mercury concentrations. Urinary gamma glutamyl transferase correlated with urinary mercury levels in the exposed group. The prevalence of greater than normal activities of the enzymes, N-acetyl-β-glucosaminidase and gamma glutamyl transferase, appeared to increase when the mercury concentration in urine exceeded 100 µg Hg/g creatinine, but there was no evidence of a dose-response relationship over the full range of mercury concentrations. These authors were not able to confirm the findings of Buchet et al. (1980) of an increased prevalence of elevated urinary albumin despite the fact that mercury values were comparable in the two studies. (The mean value in Buchet et al's. (1980) group of workers was 59 µg Hg/g creatinine, and the range of individual values was 5 to 206 µg Hg/g creatinine.)

A recent case-report study of two workers exposed to inorganic mercury (probably in the form of mercury vapor) indicates that the proteinuria consisting of large-molecular-weight proteins is due to a glomerular nephritis resulting from immunopathologic action (Weening et al., 1978). Immunohistochemical studies demonstrated confluent, finely granular epimembranous deposits of IgG and C3 antibodies in the glomerulus.

Lauwerys et al. (1983) recently found further evidence that mercury vapor may lead to immune dysfunction with the possibility of immune glomerular nephritis. In 62 workers exposed to mercury for an average of 5.5 years, circulating anti-laminin antibodies were found in the sera of eight workers whereas none were found in the sera from 60 matched controls (laminin is a non-collagenous protein isolated from basement membranes). The urinary mercury excretion in µg/g creatinine was 1.0 ± 1.1 (SE) in the controls, 53 ± 7 in the workers without anti-laminin, and 77 ± 25 in the eight workers with anti-laminin. It should be noted that several parameters of renal function did not differ between the exposed and the control groups or between the groups with and without anti-laminin.

Experiments in animals given inorganic salts of mercury confirm an immunopathological mechanism underlying the glomerular damage (Bariety et al., 1971; Druet et al., 1978, 1982; Weening et al., 1978). The nature of the antigen is not known, but a recent report by Druet et al. (1982) suggests that mercury may act directly in the immunoregulatory mechanism. Earlier studies by the same group suggested a genetic control of susceptibility of the disease in an inbred strain of rats, thus, explaining the original suggestion of Kazantzis et al. (1962).

Exposures in mercury cell chlor-alkali plants are to mixed mercury vapor and chlorides of mercury. If an ultraviolet mercury vapor instrument is used to measure exposure, that portion of the total exposure due to chlorides will be missed. Some of the studies reviewed above used ultraviolet instruments, e.g., Buchet et al. (1980). However, it should be noted that the overwhelming percentage of mercury in the working environment of chlor-alkali plants is present as vapor. Kazantzis et al. (1962) reported that exposure was to both the vapor and to compounds of mercury. Thus, it is possible that exposure to the inorganic salts of mercury may have played a role in the development of the nephrotic syndrome in some, but probably not all, of the reports reviewed above. Animal experiments, reviewed above, indicate that the nephrotic syndrome can be elicited by dosing animals with inorganic salts of mercury.

5.1.2.4. Reproductive and Developmental Effects--Little information is available on biological effects in humans due to prenatal exposure to mercury vapor. Unfortunately, in the few human studies in the literature, details on methodology and on dose and duration of exposure are not provided. Early studies suggested that women chronically exposed to mercury vapor experienced increased frequencies of menstrual disturbances and spontaneous abortions; also, a high mortality rate was observed among infants born to women who displayed symptoms of mercury poisoning (Laraview, 1956; cited in Baranski and Szymczyk, 1973). It should be noted, however, while the degree of exposure of these women was unknown, it must have been fairly high in order for symptoms of mercury poisoning to be manifested. (Laraview, 1956; cited in Baranski and Szymczyk, 1973). In 1967, an epidemiological survey in Lithuania called attention to an increased incidence of abortion and mastopathy related to duration of time on the job among women working in dental offices where mercury vapor concentrations ranged up to 0.08 mg/m^3 (Wiksztrajtis, 1967; cited in Baranski and Szymczyk, 1973). Another report described the case of a woman chronically intoxicated by mercury vapor in whom two pregnancies ended unfavorably. After recovery from overt mercury poisoning, this woman gave birth to a healthy child (Derobert and Tara, 1950). The most recent citation available (Mishonova et al., 1980) reports a study on the course of pregnancy and parturition in 349 women exposed via inhalation to metallic mercury vapors in the workplace as compared to 215 non-exposed women. The investigators concluded that the rates of complications of pregnancy and labor were higher among exposed women and depended on "the length of service and concentration of mercury vapors." Insufficient detail was available to evaluate dose-response relationships.

Baranski and Szymczyk (1973), reported that female rats, after being exposed for 21 days to an average of 2.5 mg Hg/m^3 (6 hr/day, 5 day/week), had longer estrus cycles than non-exposed animals. In addition, their mercury-induced cycles were longer than their original cycles prior to exposure. The initial phase of the cycle was protracted, but complete inhibition of the cycle did not occur. These animals, in the second and third weeks of exposure, developed signs of mercury poisoning which included restlessness, attacks of chronic seizures, and trembling of the entire body. The authors speculated that the effects on the estrus cycle were due to the action of mercury on the central nervous system.

Rats exposed prenatally to mercury vapor were reported to have died within six days after birth (Baranski and Szymczyk, 1973). In one experiment where exposures were continued throughout gestation, all of the pups died. Some of the deaths could be attributed to a failure of lactation of the dams. However, in the second part of the experiment which exposed the dams only prior to the time of impregnation, lactation and nursing of viable pups appeared normal yet, 25 percent of the pups died before day 6. No teratologic effects were observed, birth weights were reportedly within the normal range, and histopathologic findings were negative although the concentrations of vapor were high (2.5 mg Hg/m^3, the LC_{25} for the adult females) (Baranski and Szymczyk, 1973).

In a study by Khayet and Dencker (1982), the placental transport of mercury in pregnant mice and its localization in the embryo and fetus from early organogenesis through the whole fetal period was studied by whole-body autoradiography and gamma counting. Metallic mercury ($^{203}Hg^{\circ}$) after inhalation was compared to inorganic mercury ($^{203}HgCl_2$) after intravenous injection. The authors reported that the Hg° appeared to be oxidized to Hg^{2+} in the fetal tissues and that Hg° inhalation resulted in about 4-fold higher fetal mercury concentration than Hg^{2+} injection (9.9 versus 2.4 percent gram dose per gram tissue).

5.1.2.5. Mutagenic and Carcinogenic Effects--Carcinogenesis in humans has not been associated with occupational exposure to mercury vapor (Leonard et al., 1983). However, it should be noted that group sizes in health effect studies of mercury vapor-exposed workers have been small; the largest epidemiological study reported to date (Smith et al., 1970) involved 600 workers.

Aneuploidy and other chromosomal aberrations have been observed in lymphocytes from whole blood cultures of workers occupationally exposed to mercury, including people working with mercury amalgams (Verschaeve et al., 1976; Popescii et al., 1979).

Mutagenic effects in experimental test systems have not been reported for mercury vapor; whether such tests have been conducted is unknown. Cancer or tumors in animals exposed to mercury vapor have not been reported.

5.1.2.6. Other Effects--A wide variety of adverse health effects have been reported in historical accounts of cases where mercury vapor concentrations must have been very high (Ramazzini, 1713). In one such account, mercury miners were noted to be "the subjects of asthma" (Ramazzini, 1713).

In 1943, Atkinson found a new physical sign of exposure to mercury vapor which he termed "mercurialentis." He described mercurialentis as being a change in the lens of the eye consisting of a discoloration of the anterior capsule which exhibits a light reflex varying in intensity from light brown to coffee brown. He noted that the change was bilateral and symmetrical and was usually accompanied by fine punctate opacities in each lens, especially in the anterior capsule. Visual acuity was reported to be unaffected. In mercurialentis, the discoloration of the lens capsule appears a long time before the onset of signs of mercury poisoning and is therefore of value in early detection of exposure to atmospheric mercury. Mercurialentis has also been described in other groups exposed to mercury vapor (Locket and Nazroo, 1952; Rosen, 1950; Smith et al., 1970).

Biochemical changes due to exposure to mercury vapor have rarely been reported. Lauwerys and Buchet (1973) reported that, in workers exposed to mercury vapor concentrations of less than 0.05 mg Hg/m^3, plasma galactosidase, catalase, and erythrocyte cholinesterase activities were affected. Buchet et al. (1980) reported that the prevalence of increased levels of serum β-galactosidase activity in plasma increased with increasing mercury concentrations in urine. Studies on mercury-exposed workers indicate no change in red blood cell glutathione levels due to mercury (Wada et al., 1969; Rentos and Seligman, 1968).

5.2 OTHER FORMS OF MERCURY

5.2.1 Inorganic Mercury Compounds

Salts of mercuric mercury can produce acute renal failure when ingested as a single dose; the lethal dose of $HgCl_2$ in human adults has been estimated to be approximately 1 to 4 g (Gleason et al., 1957). (For a more detailed description of the effects of inorganic mercury compounds in humans and animals, see United States Environmental Protection Agency, 1984.) The inducement of effects in rats given acute doses of $HgCl_2$ were found to be temperature sensitive (Burgat-Sacaze et al., 1982). Information is lacking on chronic human exposures and on animals repeatedly dosed with compounds of inorganic mercury. It is assumed that mercuric mercury (Hg^{++}) is the proximate toxic species in mercury vapor poisoning and that differences in effects represent differences in initial tissue deposition of the two forms of mercury. Given the small amount of translocation of Hg^{++} across the blood-brain and placental barriers, inorganic salts are less likely to affect the central nervous system and the fetus than are mercury vapor exposures. The work of Druet and co-workers (1978; 1982) (see Section 6.1) indicates that, in experimental animals, the main effect of chronic exposure is damage to the kidney, produced by an immunological mechanism.

Barber (1978) reported that two workers in a mercuric oxide manufacturing plant developed neurological changes suggestive of the syndrome of amyotrophic lateral sclerosis (ALS). The sural nerves of these workers showed markedly distal latencies and slow conduction velocities. Three months after removal from work, the neurological examinations and electromyelograms of the workers were completely normal. An additional nineteen workers developed signs and symptoms that were considered to be an early phase of the neurotoxic effects of ALS and might have progressed to the full ALS syndrome. The neurological effects in these workers also proved to be reversible. The workers were exposed to mercuric oxide particles and to mercury vapor. Air levels, checked at a later date, were in the range of 0.5 to 5 mg Hg/m^3 with peaks to 10 mg Hg/m^3 as total mercury. It was stated that exposures were predominantly to mercuric oxide and were for periods of 60 to 80 hours per week.

In case reports on two adult females who had chronically ingested mercurous chloride for many years as a laxative (two tablets of 125 ng Hg_2Cl_2/day) Davis et al. (1974) and Wands et al. (1974) noted that the women developed classic symptoms of mercurialism. Both patients suffered from chronic renal failure. Death in one case was due to pneumonia; the other patient died following surgical operation for intestinal bleeding. The brains of both patients were small and showed loss of cerebellar granular cells. The cerebrums of occipital cortex were normal as scanned by light microscopy. Timm's silver stain revealed many punctate granules thought to be deposits of mercury in the cytoplasm of neurons. Deposits of mercury observed in the colon and renal cortex were identified as crystals of mercuric sulfide.

Children exposed to salts of inorganic mercury may develop acrodynia or Pink's disease (Cheek, 1980). The signs and symptoms include bluish-pink hands and feet, crimson cheeks, profuse sweating, painful joints, photophobia, glove and stocking paresthesias, irritability and other nervous disturbances. Although only a small fraction of children exposed to inorganic mercury develop the full syndrome of acrodynia, it is possible that large numbers may suffer the incomplete and clinically unrecognized syndrome.

Parenteral administration of salts of inorganic mercury produce teratological abnormalities in experimental animals. Gale (1981) reported a variety of abnormalities including edema, retardation, ventral wall defects, pericardial cavity distension, cleft palate, hydrocephalus, and heart defects in hamster fetuses given a single subcutaneous dose of mercury acetate (15 mg/kg) on the 8th day of gestation and killed on the 12th to 15th day. These findings confirm previous reports of experimental teratogenesis in hamsters given inorganic (mercuric acetate) or organic (phenylmercury acetate) compounds of mercury. The human relevance of these experimental findings, in which highly toxic doses were delivered to animals via parenteral administration, is wholly unknown.

Grin et al. (1981) studied pregnant rats following 24-hour inhalation exposure to varying concentrations of a mixture of mercury-containing salts. No methods of any procedures were included in this report; thus, interpretation of results is not possible. In a similar manner, Govorunova et al. (1981)

studied pregnant rats following 24-hour inhalation exposure to mercuric diiodide. Again, lack of any reported methodology precludes interpretation of results.

Mercuric salts *in vitro* enhance viral transformations of hamster cells and reduce the molecular weight of DNA in Chinese Hamster Ovary cells, but do not produce mutagenesis in non-mammalian cells. Mutagenic responses in mammalian cell cultures have been equivocal (for recent reviews, see Heck and Costa, 1982 a and b; Christie and Costa, 1983). As is the case with the teratogenic effects, the relevance of these findings to effects on human health is unknown.

5.2.2 Methyl Mercury Compounds

Methyl mercury and other short-chain alkylmercurials primarily damage the central nervous system in man. (For a more detailed description of the effects of methyl mercury on the adult and on developing humans, see World Health Organization, 1976; Nordberg, 1976; United States Environmental Protection Agency, 1980, 1984; Rodier, 1983). The mildest cases of poisoning are manifested by non-specific symptoms such as paresthesia, malaise and blurred vision. These symptoms usually appear after a latent period of weeks to months during chronic low-level exposures or following acute high-level exposures. The more severe cases present signs of bilateral constriction of the visual fields, deafness, dysarthria and ataxia. The most severe cases suffer from mental derangement and coma, and the outcome is often death. Methyl mercury destroys neuronal cells in areas of the central nervous system concerned with sensory and coordination functions.

Prenatal life is the most sensitive stage of the life cycle to methyl mercury. In the 1955 mercury poisoning outbreak in Minamata, Japan, severe brain damage was described in infants whose mothers, during pregnancy, had ingested fish contaminated with methyl mercury (Harada, 1968). Similar cases of severe brain damage were reported in the 1971-72 outbreak of methyl mercury poisoning in Iraq (Amin-Zaki et al., 1974). In such poisonings, damage is widespread to the developing central nervous system and probably involves derangement of basic developmental processes such as neuronal migration (Choi et al., 1978; Matsumoto et al., 1965) and neuronal cell division (Sager et al., 1982).

In more recent follow-up studies of the Iraq outbreak, Marsh et al. (1979, 1980) reported milder effects at lower maternal exposures than those reported by Amin-Zaki et al. (1974). These effects manifested as delayed achievement of developmental milestones and mild neurological abnormalities. In a Canadian study, Eyssen et al. (1983) also noted developmental delays and mild or questionable psychomotor retardation in prenatally exposed children at methyl mercury concentrations in maternal hair lower than those reported by Marsh et al. (1980). In the Canadian study, effects were not seen in prenatally exposed female children.

Mechanisms of action of methyl mercury on both the adult and developing nervous system have been recently discussed in review articles (Clarkson, 1983; Mottet and Ferm, 1983; Rodier, 1983). The reason for the long latency prior to the manifestation of clinical effects and for the selective action in certain areas of the adult brain is still not understood. Experimental work indicates that protein synthesis is disrupted in neuronal cells before overt signs of intoxication appear. The selective damage to granular cells as contrasted to the purkinje cells of the cerebellum has been attributed to the experimental findings that protein synthesis recovers in the latter, but not in the former, class of cells. It is reasonable to purpose that the greater sensitivity of the developing nervous system to methyl mercury arises from action on processes unique to the developing brain, e.g. cell division and cell migration. Methyl mercury is known to be a mitotic inhibitor that damages microtubules and is known to bind to tubulin, a protein component of microtubules. Cell division and cell migration both require intact microtubules for normal functioning and, therefore, have been suggested as primary targets for methyl mercury disruption in the developing nervous system.

Other less noted toxic effects of methyl mercury compounds include kidney and teratogenic and reproductive effects (see review by the United States Environmental Protection Agency, 1984).

5.2.3 Phenylmercury and Related Compounds

A wide variety of other organic mercury compounds have been manufactured for various purposes (fungicides, diuretics, antiseptics, contraceptives). In general, these organo-mercury compounds undergo cleavage of the carbon-mercury bond in mammalian tissues, resulting in the release of inorganic mercury. Gage (1973) has published evidence that phenylmercury is first hydroxylated by liver microsomal enzymes and that this hydroxylation is followed by a nonenzymic breakdown to phenol and inorganic mercury.

In a recent exposure of an estimated 6000 infants to a phenylmercury compound, Astolfi and Gotelli (1981) reported that several infants developed acrodynia. In contrast, Goldwater (1973) found no evidence of toxicity in 13 workers employed for 11-23 years in the manufacture of phenylmercury. Exposure levels were not reported but urinary concentrations of mercury varied from 85-100 μg/l. Cotter (1947) found liver damage in ten subjects exposed to phenylmercury salts, but other substances may have been involved in the exposure. Renal damage and intestinal complaints have been reported (see review by Skerfving and Vostal, 1972). In general, there seems to be no difference in the toxicity of various phenylmercurials which have been studied. The symptoms, where noted, resemble those of inorganic mercury. According to clinical evidence (Biskind, 1933), phenylmercury compounds, when applied topically to the skin, can produce signs of toxicity. Delayed-type hypersensitivity has been reported from skin contact with phenylmercury compounds (Mathews, 1968).

Phenylmercury acetate was widely used as a spermicidal contraceptive administered vaginally in a gel. Enhanced urinary excretion of mercury is believed to result from the vaginal absorption of phenylmercury, but no adverse health effects have been reported from use of the contraceptive (for review, see Goldwater, 1973).

In an animal study by Fitzhugh et al. (1950), rats were fed phenylmercury acetate as well as mercury acetate for 2 years. Daily intakes for the phenyl compounds were estimated to equal approximately 0.005, 0.025, 0.125, 0.50, 2.0, and 8.0 mg/kg/day. Growth was retarded at 2 mg/kg in both sexes, while 0.5 mg/kg retarded growth in males. As little as 0.025 mg/kg resulted in detectable kidney damage in the form of coagulative necrosis of the convoluted tubules in females. In males, effects were detected at 0.125 mg/kg. By contrast, the smallest dose of mercuric acetate causing detectable effects was 2 mg/kg/day. Tryphonas and Nielsen (1970) fed weanling piglets phenylmercuric chloride at daily doses equivalent to 0.19, 0.38, 0.76, 2.28, and 4.56 mg/kg body weight. Decreased weight gain, but no pathological lesions, were detected in the 0.76 mg/kg group. Weight loss, diarrhea, necrosis of intestinal walls and kidney pathology were the primary effects detected at the two highest doses.

Very little information is available concerning the effects of phenylmercury compounds upon the nervous system. In the study by Fitzhugh et al. (1950), no neurological effects were reported in rats even after they were fed phenylmercury acetate for 2 years at daily doses as great as 8 mg/kg/day. In a similar study with pigs, doses of phenylmercury chloride up to 4.56 mg/kg/day, which produced definite kidney injury, were not reported to affect the nervous system (Tryphonas and Nielsen, 1970).

The only teratogenic information on phenylmercury compounds was reported by Gale and Ferm (1971), in which Syrian golden hamsters were intravenously dosed with 5, 7.5, 8 and 10 mg/kg phenylmercuric acetate on the eighth day of gestation. With the exception of the lowest dose, all other doses induced increased resorption rates and edema along with a few miscellaneous abnormalities, including exencephaly, cleft lip and palate, and rib fusions.

5.3 INTERACTIVE RELATIONSHIPS

Goldwater (1964) emphasized the importance of "host factors" in determining human exposure to mercury vapor. He warned that "undue preoccupation with an agent (i.e., inhaled mercury vapor) or the environment to the exclusion of interest in the host may retard progress in unravelling some of the mysteries about the effects of mercury vapor on man." He noted that, in any individual case, there was not likely to be a correlation between mercury content (of blood and urine) and clinical evidence of poisoning. He noted Zbinden's list of seven unrelated factors which could affect the outcome of animal toxicity experiments, namely: diet, sex, age, spontaneous diseases, environment, heredity and endocrine status. Of these, genetic factors have already been discussed in determining nephrotoxicity of mercury vapor. In general, these host factors have not been explored either epidemiologically or experimentally.

However, it should be noted that the potential of these seven "unrelated factors" in affecting an individual's response to mercury must be viewed in regard to the fact that dose-response relationships in humans have been demonstrated for mercury vapor and methyl mercury compounds. These unrelated factors are not so confounding as to completely undermine estimates of risks from known exposures or levels of mercury in indicator media, at least on the group basis, nor is there evidence to indicate that mercury toxicity is more influenced by these "host factors" than other toxicants.

5.3.1 Inhaled Mercury Vapor Versus Other Forms of Mercury

The central nervous system is the principal target tissue for both inhaled mercury vapor and ingested methyl mercury compounds. These are the two forms of mercury to which human populations are principally exposed. Unfortunately, no studies have been reported on the effects of exposure to both forms of mercury. From a biochemical viewpoint, additive interaction between these two forms of mercury is, at least, a theoretical possibility as evidenced by the intensive neurophysiological and neuropsychological studies conducted by Vroom and Greer (1972) on nine thermometer workers. These workers showed typical signs and symptoms of mercurialism that led the authors to conclude that "severe inorganic mercury poisoning may produce many of the abnormalities associated with organic mercury poisoning". Vroom and Greer noted that memory loss, tremor, rigidity, and truncal unsteadiness were common to both forms of poisoning, suggesting that the same areas of the brain (the cerebellum and temporal lobes) may be affected when exposed to the different forms of mercury. However, it should also be noted that in the early stages of poisoning, the effects of mercury vapor and of methyl mercury are not similar.

Both inhaled mercury vapor and methyl mercury are transformed to divalent inorganic mercury (Hg^{++}) in mammalian tissues. It is possible, but not proven, that Hg^{++} may be the proximate toxic species to the central nervous system for both forms of mercury (for discussion, see Clarkson, 1983; Shamoo, 1982).

5.3.2 Other Factors Affecting the Toxicity of Inhaled Vapor

The previous section has described the effects of moderate doses of ethanol on the metabolism of inhaled mercury vapor. One effect is that individuals who have ingested ethanol retain substantially less inhaled mercury vapor. On the other hand, ethanol allows dissolved mercury vapor to persist in plasma for longer periods of time and, therefore, the potential of mercury vapor to penetrate the central nervous system increases. Indeed, Hamilton (1925) noted that alcoholism greatly favored the development of tremor and that no total abstainer ever suffered from tremor in the severe form.

The interaction of inhaled mercury vapor with selenium compounds in the body may also possibly affect the toxicity of mercury vapor. In autopsy tissue from mercury miners in Idria (Yugoslavia), it was noted that the atomic ratio of mercury to selenium was constant at a value of 1:1 (Kostial et al., 1975). Tubbs et al. (1982) noted an association between mercury and selenium in tubular epithelial phagolysosomes in nephrotic kidneys of individuals exposed to mercury vapor.

5.4 SUMMARY

The toxic effects of mercury and its compounds depend upon the chemical form of mercury. The four major forms of mercury to which humans are exposed are mercury vapor, compounds of methyl mercury, inorganic divalent mercury, and phenylmercury. Each of these four major chemical classes of mercury elicits characteristic toxic effects.

Mercury vapor primarily damages the nervous system, but effects are seen, depending on the doses, on the oral mucosa and on the kidneys. Effects on the nervous system are manifested as tremor and erethism. Some of the earliest effects seen are deficits in short-term memory and introversion. The peripheral nervous system may also be involved, as evidenced by electromyographic changes. The effects on the nervous system are usually reversible, especially those on motor functions. The more insidiously developing cognitive decrements and emotional alterations may be the most harmful in light of current exposures in the workplace.

Mercury vapor can elicit the nephrotic syndrome characterized by excess loss of protein (mainly albumin) in the urine and edema. Differences in individual susceptibility appear to be great. Lower levels of exposure to mercury vapor are associated with mild proteinuria and enzymeuria which are reversible.

Limited information is available on the effects of mercury vapor on the early stages of the human life cycle. One report in the foreign literature (Mishonova et al., 1980) reported effects on pregnancy and parturition in women occupationally exposed to mercury vapor; insufficient detail was available to evaluate dose-response relationships.

Inorganic divalent mercury compounds are corrosive poisons; acute single doses can cause death by kidney failure and systemic shock. Little information is available on the chronic effects of inorganic mercury compounds in humans. Occupational exposure to mercuric oxide has been shown to damage the peripheral nervous system and to produce effects somewhat similar to amyotrophic lateral sclerosis; however, these effects are reversible. Exposure to inorganic divalent mercury compounds has been noted to produce acrodynia (Pink's disease) in children.

Methyl mercury compounds mainly damage the nervous system. In human adults, the damage is selective to certain areas of the brain concerned with sensory and coordination functions, particularly neurons in the visual cortex and granular cells of the cerebellum. Effects such as constricted visual fields and ataxia appear to have a latent period of weeks to months. Such effects are usually irreversible. The first effect usually noted is a subjective complaint of paresthesia in the extremities and in the circum-oral region. Paresthesias may or may not be irreversible. The peripheral nervous system may also be affected, especially at high doses, but usually after effects have already appeared in the central nervous system.

The prenatal stage is the most susceptible stage of the human life cycle to methyl mercury exposure. Severe effects, such as cerebral palsy, may be seen in the offspring from mothers whose effects have been minimal or absent. The milder effects seen at lower exposures are psychomotor retardation. All prenatal effects that have been followed to date are irreversible.

Despite widespread use of phenylmercury compounds, little is known about their human toxicology. Liver damage has been reported after occupational exposure. These compounds are rapidly metabolized to inorganic mercury in the body. This may explain why they produce similar effects such as acrodynia in children and mild kidney damage in experimental animals. It is not known whether phenylmercury compounds produce prenatal effects in humans.

Generally speaking, mercury and its compounds are not mutagenic. Despite widespread and long-term human exposures, no carcinogenic actions have been reported.

6. HUMAN HEALTH RISK ASSESSMENT OF MERCURY IN AIR

6.1 AGGREGATE HUMAN INTAKE

The estimates of human intake and retention of mercury and its compounds presented in this chapter are based on levels of mercury in air, water, and food discussed in Chapter 3 and on the efficiencies of pulmonary or gastrointestinal absorption presented in Chapter 4. These estimates are summarized in Table 6-1 and are discussed in more detail below.

TABLE 6-1. ESTIMATED AVERAGE DAILY INTAKE (RETENTION)[a] OF MERCURY COMPOUNDS IN THE U.S. POPULATION NOT OCCUPATIONALLY EXPOSED TO MERCURY

Exposure	Estimated mean daily intake, ng Hg/day (retention)		
		Compounds of Mercury	
	Mercury vapor	Inorganic	Methyl
Atmosphere	120(96)	38(30)	34(27)
Food			
Fish	-	940(94)	3760(3572)
Non-fish	-	20,000(2000)	
Drinking water	-	50(5)	-
Total	120(96)	20,978(2124)	3794(3599)

[a] For assumptions underlying the calculations of average daily intake and retention, see text. The numbers in parentheses represent the estimated amount retained in the body of an adult.

6.1.1 Inhaled Mercury Vapor

Evidence was presented in Section 3.3.1 that background levels of total mercury in the Northern Hemisphere are 2 ng Hg/m^3. Regionally polluted rural areas often lie between 3 and 4 ng Hg/m^3 and urban areas may have average concentrations as high as 10 ng Hg/m^3. Rarely will mercury concentrations exceed average values of 50 ng Hg/m^3. For purposes of calculation, the average atmospheric level of total mercury to which humans are exposed is assumed to be 10 ng Hg/m^3. Unfortunately, there is considerable uncertainty with regard to qualitative speciation of mercury in the atmosphere, although it is generally accepted that the major fraction is in the form of mercury vapor. While recognizing the possible limitations of the Johnson and Braman (1974) data (see Section 3.3.1), it is, nevertheless, possible to calculate daily air intakes from these data. Assuming that 60 percent of mercury in the atmosphere is in the form of vapor, 19 percent is inorganic ionic mercury, and 17 percent is methyl mercury compounds, and assuming a daily ventilation rate of 20 m^3 for the average adult and 80 percent retention of all forms of mercury, various air intakes can be derived for different mercury species (Table 6-1). Because particulate matter accounts for such a small percentage of total atmospheric mercury (4 percent), intake calculations for this form of mercury have not been included in Table 6-1.

6.1.2 Other Forms of Mercury

In Section 3.3.3 average human intake of total mercury from drinking water was calculated to be approximately 50 ng/day. This figure was based on the review by Fitzgerald (1979) that reported average concentrations of 25 ng Hg/ℓ in drinking water. Assuming that the average consumption in adults is 2 ℓ/day and assuming that gastrointestinal absorption is around 10 percent (see Section 3.3.3), the estimated daily retention of mercury from drinking water is approximately 5 ng (Table 6-1). This value may be overestimated, however, in light of the most recent review by Jernelov et al. (1983), which states that data from freshwater studies in Sweden suggest that the true average of mercury in water is less than 25 ng/ℓ and may be as low as 3 ng/ℓ.

Most reports indicate that the proportion of methyl mercury in samples from bodies of natural water is very small, frequently beyond the limit of detection (Brouzes et al., 1977). It is not known to what extent the findings of a recent report (Kudo et al., 1982), that 30 percent of mercury in water is methyl mercury, apply to mercury in drinking water. The figures reported in Table 6-1 are based on the assumption that all mercury in drinking water is in the form of Hg^{++} (for further discussion, see Section 3.3.3).

In Section 3.3.4 average human intake of mercury from various food sources is discussed in greater detail. The food figures reported in Table 6-1 are based on data presented in Table 3-2 in Chapter 3. An estimate was made of the total mercury intake from fish and seafood and this number was divided by the total number of fish consumers to yield an average daily intake of 4.7 μg Hg for an adult fish consumer living in the United States. The estimates presented in Table 6-1 are based on the assumption that 80 percent of the total mercury in edible fish and seafood tissues is in the form of methyl mercury compounds and that the remainder is as inorganic mercury compounds. Of these compounds, 95 percent of the methyl mercury and 10 percent of the inorganic mercury is absorbed and retained.

Non-fish food items are assumed to contain an average mercury concentration of 10 ng Hg/g fresh weight, all in the form of inorganic mercury compounds (see Section 3.3.4). The retention of inorganic mercury is assumed to be 10 percent of the amount ingested in food. Assuming that a standard 70-kg adult consumes 2 kg of food per day, total daily intake of inorganic mercury is estimated as 20,000 ng Hg and total retention as 2000 ng Hg (Table 6-1). It should be noted that this calculation is subject to large error as the "background" level of mercury in non-fish food items (here assumed to be 10 ng/g) is frequently below the limit of detection.

The total average daily intake of all forms of mercury (methyl mercury and inorganic) from food, given in Table 6-1, may be estimated to be 24.7 μg (20,000 + 940 ng Hg as inorganic mercury and 3760 ng Hg as methyl mercury). This may be compared with a figure of 13 μg Hg calculated as the average daily intake of total mercury in food for the population of Belgium (Fouassin and Fondu, 1978). Fouassin and Fondu based their measurement of total mercury on 2500 samples of various food items and on food production figures and import and export statistics for Belgium. Buchet and co-workers (1983) made direct measurements of mercury intake from food and beverages by analyzing mercury in one hundred and twenty four daily meals collected in three areas of Belgium. The median total mercury intake from food was 6.5 μg. The distribution was not normally distributed since the arithmetic average was 13 μg/day. Two diets exceeded the FAO/WHO (1972) tolerable provisional weekly intake of 5 μg/kg body weight (i.e., 50 μg Hg/day for a 70-kg adult) with values of 80 and 497 μg kg/day.

As presented in Table 6-1, the average daily intake of total mercury from fish and seafood is 4.7 μg Hg (940 ng Hg as inorganic mercury and 3760 ng Hg as methyl mercury). Fouassin and Fondu (1978) estimated the average daily intake of total mercury from fish in the Belgian population to be 2.9 μg Hg, Bernhard and Andreae (1984) estimated the average worldwide intake from seafood to be 2 μg Hg/day, and Clarkson and Shapiro (1971) presented calculations indicating the intake of methyl mercury by U.S. adults to be 3 μg Hg/day.

A number of conclusions about atmospheric mercury may be drawn from Table 6-1: (1) atmospheric mercury accounts for approximately 6 percent of the total amount of mercury retained each day, (2) it accounts for all the mercury vapor retained each day, and (3) it accounts for approximately 2 percent of the methyl mercury retained each day. From these conclusions, it is reasonable to assume that direct inhalation of normal levels of mercury in air should not make a significant contribution to overall human body burden. The biological half-time of inorganic mercury in man is, if anything, somewhat shorter than that of methyl mercury (for details, see Chapter 4). Even assuming that all mercury in air were in the form of methyl mercury, the contribution of intake from food (fish) would still be the determining factor in accumulated body burden.

6.2 SIGNIFICANT HEALTH EFFECTS

6.2.1 Inhaled Mercury Vapor

Evidence reviewed in Chapter 5 indicates that most of the significant health effects of inhaled mercury vapor arise mainly from the action of the vapor on the nervous system. These effects may be classified according to their severity. The mild effects, which are non-specific, consist of emotional alterations, such as introversion and anxiety, and cognitive changes, such as short-term memory loss. Neurological signs, such as slight tremors, may also be present. Moderate effects, which may be partly debilitating, include pronounced tremors which begin at peripheral parts of the body, such as fingers, eyelids, and lips. Psychological disturbances, such as anxiety and memory loss, also become more pronounced, and gums may become sore. As effects become more severe, the peripheral nerves may be affected. In severe cases, delusion and hallucinations occur accompanied by excessive secretion of saliva, which may amount to 1 liter per day. A general tremor develops throughout the whole body with violent chronic spasms occurring in the extremities.

Effects on kidney function are important to individuals who are susceptible to this form of damage. The nephrotic syndrome is a serious but usually reversible health effect (see Section 5.1.2). Preclinical effects such as urinary excretion of abnormal amounts of large molecular protein, but without a fully developed nephrotic syndrome, may serve as an early warning sign. More studies are needed on this topic.

Some degree of recovery usually takes place after poisoning from mercury vapor. Motor effects, such as tremor, disappear more rapidly than the psychological effects. Very severe cases result in long-term damage to the nervous system. Baldi et al. (1953) monitored 135 cases of mercury poisoning for several years and found that only 69 improved, whereas 33 were unchanged, 28 deteriorated, and 5 died of other illnesses.

Most cases of nephrotic syndrome due to mercury poisoning gradually recover after cessation of exposure.

6.2.2 Compounds of Inorganic Mercury

Data on effects of chronic exposure to inorganic mercurial compounds are scarce. Case reports of oral intake of mercurous compounds indicate effects are the same as those reported for inhalation of mercury, with damage occurring primarily to the nervous system and the kidneys.

Acrodynia is a serious but reversible effect seen in children exposed to inorganic mercury and those organic compounds of mercury that rapidly break down to inorganic mercury in mammalian tissues, e.g., phenylmercury compounds (for details, see Section 5.2).

6.2.3 Methyl Mercury Compounds

Methyl mercury and other short-chain alkyl mercurials primarily damage the central nervous system. A range of significant health effects are produced. Mild effects are paresthesias of the extremities and circumoral areas, malaise, and blurred vision. Moderate effects include bilateral constriction of the visual fields, dysarthria, ataxia and diminished hearing. Severe cases suffer from mental derangement, coma, and complete loss of vision and hearing. The earliest effects may be reversible, although the literature evidence is conflicting on this point. The moderate and severe effects are essentially irreversible, as they result from destruction of neuronal cells in the brain. The prenatal developing central nervous system is more sensitive to methyl mercury than the mature system. Mild but significant health effects include delayed achievement of developmental milestones, seizures, and mild neurological signs. More serious effects resemble cerebral palsy and are irreversible.

6.3 DOSE-RESPONSE AND DOSE-EFFECT RELATIONSHIPS

6.3.1 Inhaled Mercury Vapor

6.3.1.1 Indices of Exposure--Urine is the most frequently used indicator medium for exposures to mercury vapor, as well as to inorganic mercury compounds, phenylmercury, and other organic mercury compounds that rapidly break down in the body to inorganic mercury. In a study sponsored by the World Health Organization and summarized by Goldwater (1972), some 1107 urine samples from fifteen countries were analyzed for mercury by the method of Jacobs et al. (1961). These samples, collected from individuals with no known exposures (either occupational or other deliberate exposures to mercury), were found to contain mercury below the limit of detection (0.5 μg Hg/l) in 78 percent, below 5 μg Hg/l in 86 percent, below 10 μg Hg/l in 89 percent and below 20 μg Hg/l in 95 percent of all samples tested. More recent reports on "control groups" in occupational and epidemiological studies confirm these findings.

The health effects of mercury vapor are almost certainly due to inhalation, although some skin absorption may occur. Under steady-state conditions, one would expect to see linear relationships between mercury levels in air and concentrations in indicator media such as blood and, particularly, urine. Indeed, Smith et al. (1970) have published graphs (Figures 6-1, 6-2, and 6-3) indicating that blood and urine concentrations of workers exposed for many years are linearly proportional to time-weighted average air concentrations of mercury vapor. The data on blood-versus-air concentrations (Figure 6-1) indicate that steady-state blood levels will increase by about 49 ng Hg/ml for each 100 $\mu g/m^3$ increase in the air concentration. The data on urinary mercury concentrations indicate that they are also linearly related to time-weighted average air concentrations; however, the slope of the line relating urine to air concentrations depends upon how the urinary mercury concentrations are expressed. Thus, uncorrected urine concentrations have the flattest slopes indicating that for every 100 $\mu g/m^3$ increase in mercury air concentrations, the urine concentration would increase about 200 μg/l (Figure 6-2). If urinary concentrations are corrected to a specific gravity of 1.024, the proportional increase in urinary concentration would be about 300 μg/l for every 100 $\mu g/m^3$ increase in mercury air concentration (Figure 6-3). The latter value is similar to other values reported in the literature.

Lundgren et al. (1967) and Hernberg and Hassanon (1971) also reported relationships between mercury in blood and mercury in urine. These relationships may be combined with the blood level versus air concentrations reported by Smith et al. (1970) to predict that the urinary concentration of mercury will increase approximately 300 μg/l for every 100 $\mu g/m^3$ increase in time-weighted average air concentration.

The above relationships were based upon the measurement of air concentrations using static samplers. Henderson (1973) was the first to report quantitative differences in mercury concentrations in the general working environment

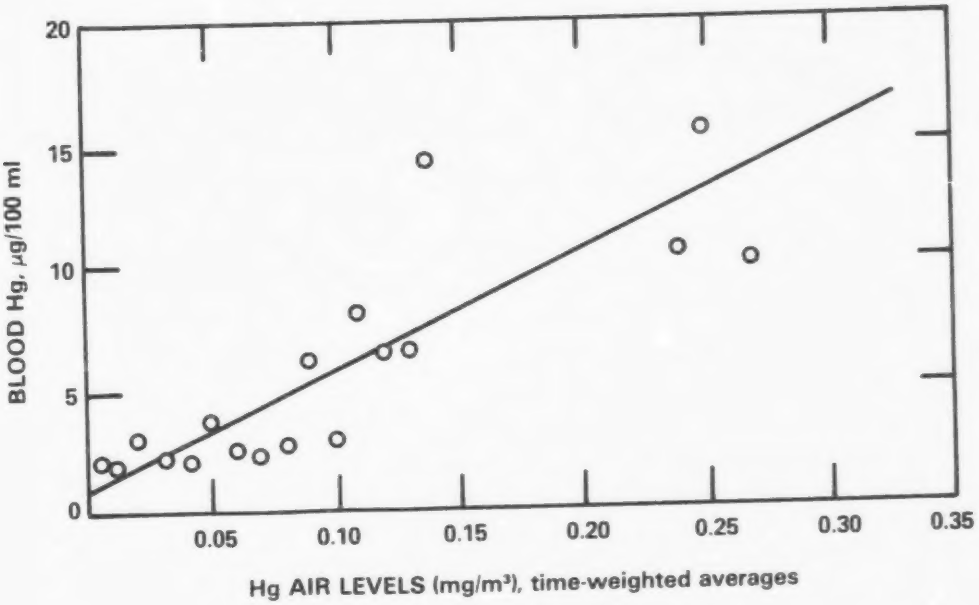

Figure 6-1. Relation of concentration of mercury in blood to the corresponding time-weighted average exposure levels.

Source: Smith et al. (1970).

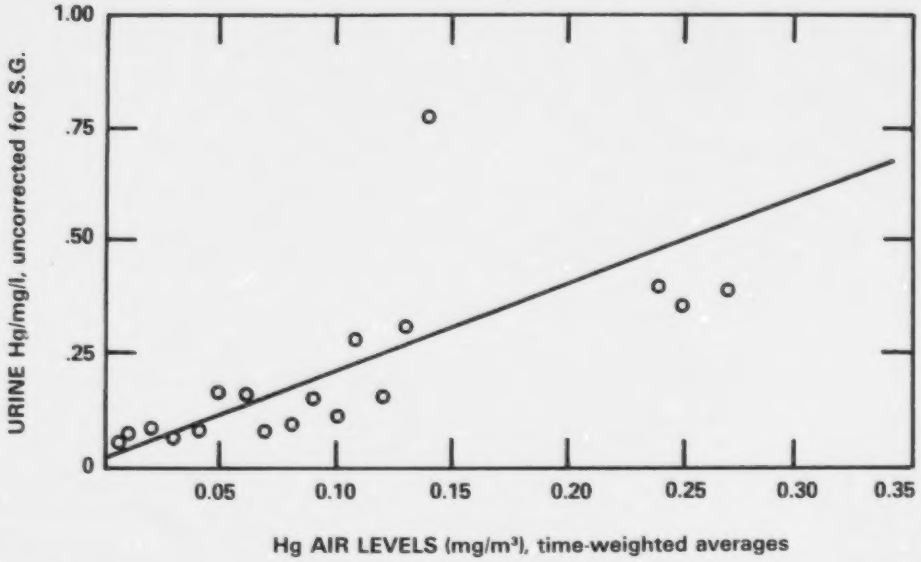

Figure 6-2. Concentrations of mercury in urine (uncorrected for specific gravity) in relation to time-weighted average exposure levels.

Source: Smith et al. (1970).

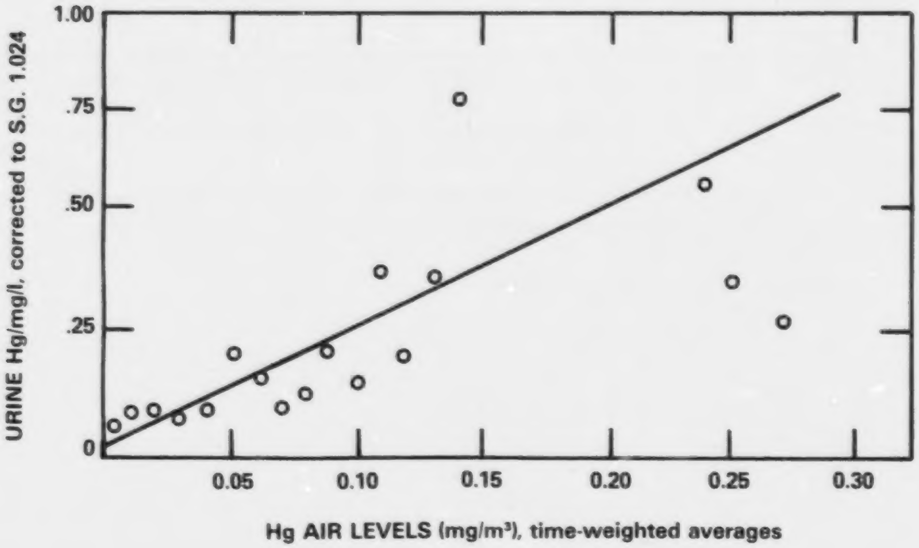

Figure 6-3. Concentrations of mercury in urine (corrected to specific gravity of 1.024) in relation to time-weighted average exposure levels.

Source: Smith et al. (1970).

compared to the "microenvironment" in the breathing zone of the individual worker. This was confirmed by Stopford et al. (1978), who noted that breathing zone samples may average several-fold higher in concentration than concurrent area samples, reflecting a "microenvironmental" contribution of exposure to mercury vapor, presumably from contaminated clothing and hands. Thus, several reports have found that when personal samplers are used, a 100 $\mu g/m^3$ increase in air concentration is associated with an increase in urinary concentration of 100 µg/l (Bell et al., 1973b), 130 µg/l (Berode et al., 1980), or 160 µg/l (Lindstedt et al., 1979), all of which are considerably lower than the increase of 300 µg Hg/l urine based on area (static sampling) levels of mercury.

Recently, a report by Schuckmann (1981) has indicated that, by intensifying compliance with personal hygiene and safety regulations and by improving technology of production in the factory, static samplers can approach the ratio of air-to-urine concentrations as observed by use of personal samplers.

These presumed steady-state relationships noted above have been based on observations on groups of workers. However, high individual variation and great fluctuations from day to day have been reported in individual workers under similar conditions of exposure (Ladd et al., 1963; Jacobs et al. 1964). Indeed, Copplestone and McArthur (1967) found no correlation between urinary concentrations and air concentrations. Their own findings and their reviews of previous publications (Jacobs et al., 1964; Neal et al., 1941) led them to propose that "mercurialism might be due to an inability to excrete absorbed mercury rather than simply due to exposure." However, subsequent studies reviewed above have not generally supported this viewpoint.

Wallis and Barber (1982) reported on the individual variability of mercury concentrations in 146 spot urine samples collected from a total of 10 men and 10 women who were occupationally exposed to mercury vapor (Figure 6-4). In this figure, the normalized values (concentration in spot urine sample divided by the 24-hour excretion) are plotted according to the 24-hour excretion rate for each individual worker. It may be seen that a wide range of normalized concentrations is found in spot samples collected on the same day for each individual and that there is no relationship between these normalized concentrations and the 24-hour excretion rate. Wallis and Barber (1982) also reported that correcting the concentration for specific gravity significantly reduced the variance in daily spot urine samples. The first sample collected after a night's rest was more representative of the composites of all spot samples collected on one day

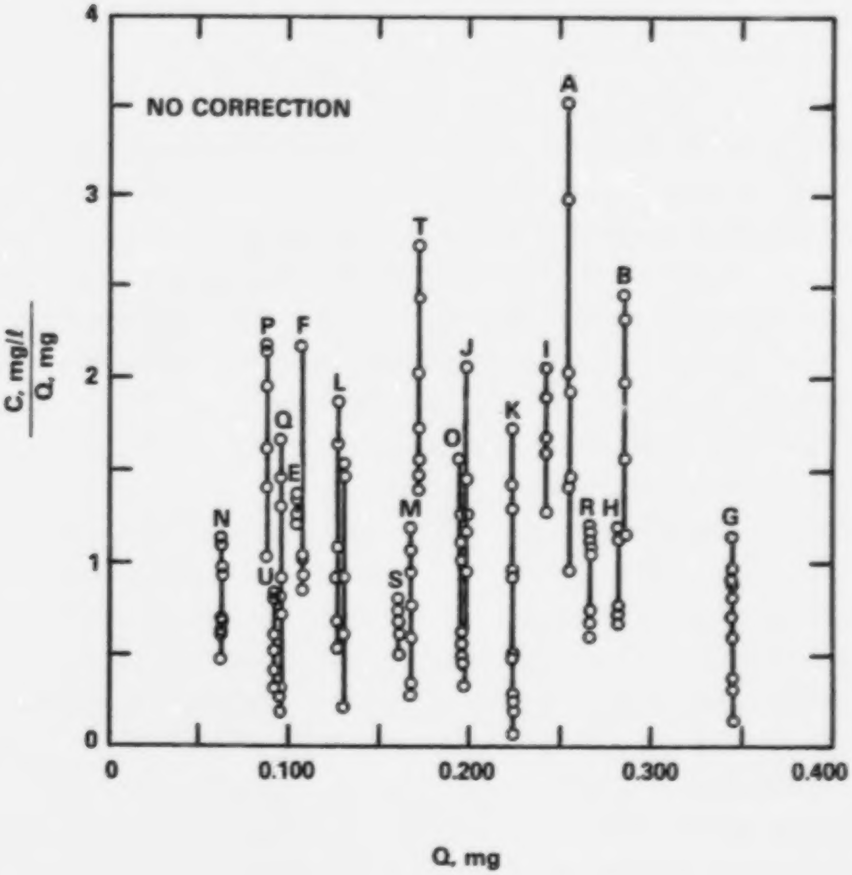

Figure 6-4. The normalized concentration of urinary mercury concentration versus the 24-hour mercury excretion.

Source: Wallis and Barber (1982).

than spot samples collected at other times. This can probably be attributed to the fact that the first spot sample of the morning typically represents a collection of from six to eight hours as compared to only two to four hours from other spot samples. Similar observations have been made by Piotrowski et al. (1975). In a follow-up publication, Barber and Wallis (1984) noted that correction of concentrations of mercury in spot urine samples for specific gravity or osmolality reduced the variability to about the same extent and that correction for creatinine was the most effective in reducing this variability.

Short-term (non-steady-state) exposures may not show consistent relationships to indices of exposure. Mercury clearance from blood is described by several exponentials. After a single dose, over 50 percent of the mercury is cleared with a half-time of a few days. A component with a half-time of about 20-30 days accounts for about 10 percent of total mercury in blood (for details, see Chapter 4). Thus, under non-steady-state conditions, blood levels of mercury may represent recent exposure.

Similarly, the relationship between urinary concentrations and air levels will be difficult to predict under circumstances of non-steady-state conditions. Piotrowski et al. (1975) reported that urinary concentrations fell according to a two-exponential equation corresponding to half-times of 2 and 70 days in workers whose exposures to mercury vapor had ceased. According to studies carried out on volunteers receiving a tracer dose of mercury vapor, mercury in urine is not directly related to blood concentrations but probably reflects the kidney burden of mercury (Cherian et al., 1978).

Indeed, many factors other than non-steady-state conditions may contribute to observed variability in urinary excretion of mercury. Roels et al. (1982) have noted that workers who smoke have higher urinary mercury levels than non-smoking workers under similar conditions of exposure. Other factors contributing to the variability could be daily changes in urinary specific gravity, problems with analytical methodology and volatilization of mercury from urine (Magos et al., 1964), and the nature of the container (Greenwood and Clarkson, 1970).

6.3.1.2. Effect and Dose-response Relationships--Dose-effect and dose-response relationships for human exposure to mercury vapor have been reviewed by a number of expert groups (World Health Organization, 1976, 1980; Nordberg, 1976; U. S. Environmental Protection Agency, 1980, 1984). Some of these relationships are presented below.

6.3.1.2 1 Effects on the nervous system. The largest study on human exposure was published by Smith et al. (1970). This involved 642 workers from 21 chlor-alkali plants in the United States and Canada. Worker exposure to mercury vapor, measured on a time-weighted average concentration in the working environment, was compared to individual medical findings and to concentrations of mercury in individual samples of blood and urine. The control group consisted of 382 workers not occupationally exposed to mercury. Both control and exposed groups had similar age distributions, smoking habits and alcohol consumption patterns. The exposure-response relationship found in this study is illustrated in Figure 6-5. A number of medical findings related to effects on the nervous system and exhibited a statistically significant relationship to exposure (Table 6-2), whereas many other medical findings (Table 6-3) did not correlate with exposure to mercury. Most strongly related to excessive exposure were the symptoms of loss of appetite and weight, insomnia, and other indicators of early effects on the nervous system, such as tremors. The authors stated there was no evidence of kidney or other organic injury. Interestingly, no statistical correlation was found between exposure and effects on the gums and teeth.

A dramatic increase in frequency of some symptoms and signs, such as loss of appetite, weight loss, insomnia, and objective tremors, took place at the highest time-weighted air concentrations (0.24 to 0.27 mg Hg/m^3). It seems unlikely that the prevalence of objective tremors was increased over the control prevalence at air concentrations below 0.1 mg Hg/m^3, but such non-specific symptoms as weight loss and loss of appetite, insomnia, and shyness may have increased at the lowest levels. The dose-response relationship depicted in Figure 6-5 does not exhibit any clear threshold.

Chaffin et al. (1973) conducted a study on 142 workers of which 75 had currently been exposed to mercury vapor and 65 had previously been exposed. Workers' urinary mercury levels were reported to range from less than 10 µg Hg/l to just above 1000 µg Hg/l. Workers were questioned about symptoms, particularly those of irritability, sleep disturbance, anorexia and weight loss. In addition, all workers' medical records were reviewed over previous work periods (3 to 10 years) in order to detect significant changes in body weight.

The authors reported that no significant weight changes occurred in any of the workers during the study period under review and that the responses of

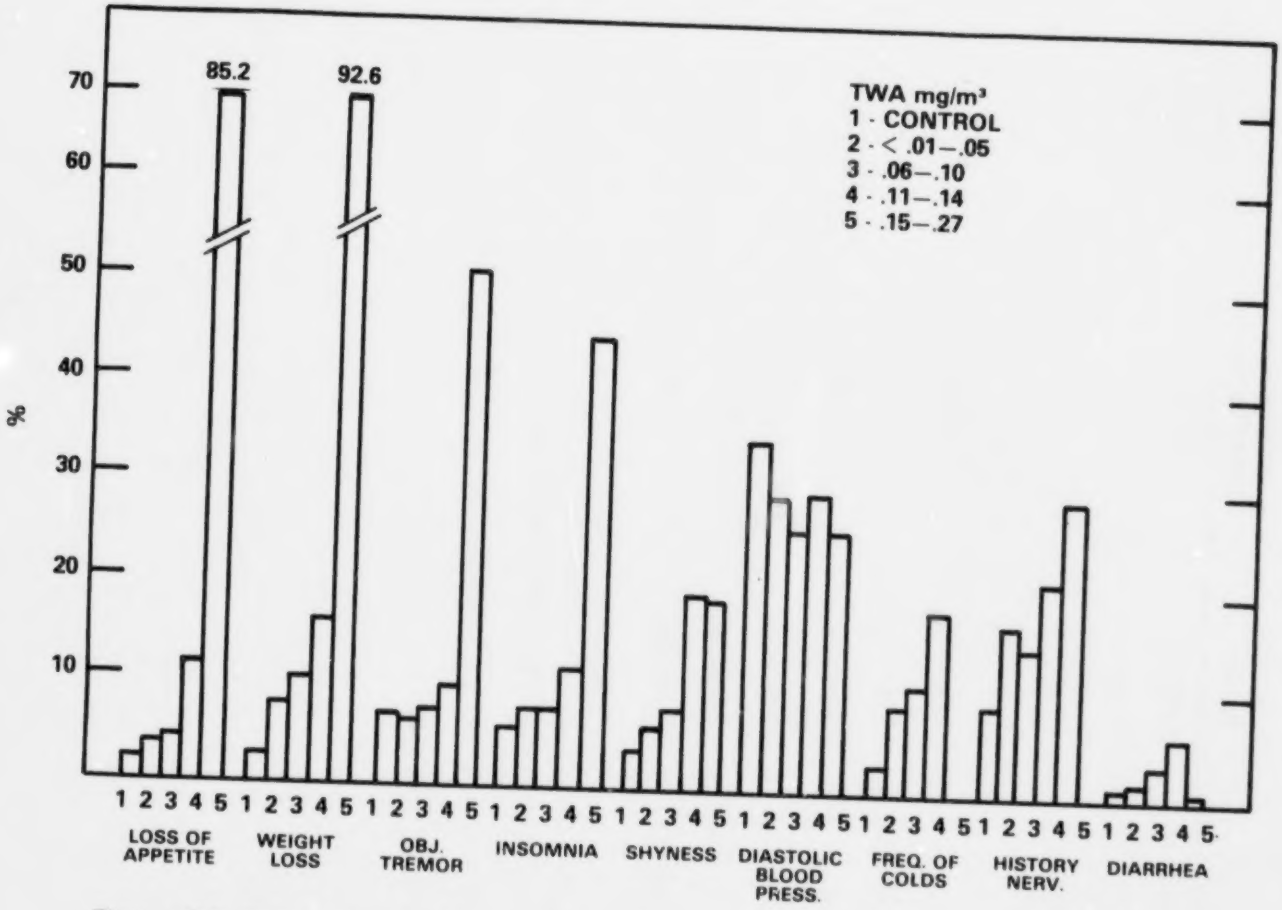

Figure 6-5. Percentage incidence of certain signs and symptoms related to exposure of workers to mercury.

Source: Smith et al. (1970).

TABLE 6-2. MEDICAL FINDINGS RELATED TO MERCURY EXPOSURE
(Based on dose-response relationship)

Findings	Basis	t-Value of correlation coefficient	Significant at P-Level
Loss of appetite	Symptom	19.55	0.001
Weight loss	Symptom	16.51	0.001
Objective tremors	Sign	7.06	0.001
Insomnia	Symptom	6.98	0.001
Shyness	Symptom	4.54	0.001
Diastol, blood pres.	Sign	-3.38	0.001
Frequent colds	Symptom	3.09	0.001
Nervousness	Symptom	2.79	0.005
Diarrhea	Symptom	2.41	0.020
Alcohol consump.	Symptom	2.33	0.020
Dizziness	Symptom	2.08	0.040

Symptoms - subjective findings, reported by patient.

Signs - objective findings, measured by physician or laboratory.

Source: Smith et al. (1970).

TABLE 6-3. MEDICAL FINDINGS NOT RELATED TO MERCURY EXPOSURE
(Based on dose-response relationship)

Findings	Basis	t-Value of correlation coefficient	Significant at P-Level
Palpitation	Symptom	1.96	0.050
Oropharyngeal	Symptom	1.83	0.070
W.B.C. count	Sign	-1.78	0.075
Cardiopulm. illness	Symptom	1.76	0.075
Subj. tremors	Symptom	1.50	0.150
Neurological illness	Symptom	1.23	0.200
Cough	Symptom	1.20	0.300
Hematocrit	Sign	1.16	0.300
Abn. teeth-gums	Sign	1.07	0.300
Tooth decay	Symptom	-0.92	0.300
Heart trouble	Symptom	-0.64	--
Chest pain	Symptom	-0.53	--
Systol. blood pres.	Sign	-0.45	--
Fatigue	Symptom	0.41	--
Abn. EKG	Sign	0.35	--
Short breath	Symptom	0.27	--
Sputum	Symptom	0.19	--
Headache	Symptom	0.17	--
Constipation	Symptom	-0.17	--
Anxiety	Symptom	0.16	--
Abn. chest x-ray	Sign	--	--

Source: Smith et al. (1970).

the workers to questions about symptoms failed to confirm the findings of Smith and co-workers (1970). It should be noted, however, that there were no identifiable controls in this study. Also, "current" blood and urine mercury concentrations were used as independent variables in the exposure analysis and those variables were noted to vary "a great deal from month to month."

Trachtenberg (1969) reported an increased prevalence of a syndrome defined as a combination of insomnia, sweating, and emotional lability in workers exposed to air concentrations in the range of 0.01 to 0.05 mg Hg/m^3 as compared to a control group with exposures less than 0.01 mg Hg/m^3. However, ambient temperatures in the working areas of exposed versus control groups were not identical and no details were given as to the selection and evaluation of these workers. In support of Trachtenberg's findings, Bidstrup et al. (1951) and Turrian et al. (1956) reported that certain psychological disturbances may occur at air concentrations below 0.1 mg Hg/m^3.

It should be noted that there is no evidence that either Trachtenberg (1969), Bidstrup et al. (1951), or Turrian et al. (1956) measured the concentrations of mercury vapor in the microenvironment of the workers; nor did they measure the possible continuing exposure beyond work hours from contaminated skin, hair, clothing, and smoking materials.

Electromyographic, neuromuscular, and psychomotor tests have been conducted on workers exposed to mercury in the chlor-alkali industry (Chaffin et al., 1973; Miller et al., 1975; Langolf et al., 1977; 1978; and Schuckmann, 1979). Miller et al. (1975) found a relationship between the mean frequency of tremor and urinary mercury concentrations, indicating effects at urinary mercury concentrations as low as 100 μg/l. Conversely, Langolf et al. (1977; 1978), using power spectral analysis, were unable to detect tremor effects at urinary concentrations below 500 μg/l. Schuckmann (1979) was unable to find psychomotor activity changes in a group of 39 workers exposed to mercury vapor in a chlor-alkali plant. The mean urinary mercury concentration of the workers was 108 μg/l in 1977, but in the period 1974-1976 it was 116 μg/l, with 8 percent of the workers between 350 and 525 μg/l and another 8 percent over 525 μg/l.

More recently, Roels et al. (1982) reported on the results of psychomotor tests on 43 workers exposed to mercury and on 47 control workers matched for age, socioeconomic status and job characteristics. The groups had similar smoking and alcohol consumption characteristics. Two psychomotor tests were used: one for testing eye-hand coordination (the orthokinesimeter test) and the other for testing arm-hand steadiness (the hole tremormeter test). No clear-cut dose-response relationship could be established between abnormal responses on these tests and concentrations of mercury in samples of blood and urine. However, although statistically not significant, there was a tendency for an increase of preclinical alterations for eye-hand coordination and arm steadiness at blood levels between 10 to 20 ng Hg/ml and urinary excretion rates greater than 50 µg Hg/g creatinine.

Thus, the studies using specific psychomotor tests are in agreement that effects are clearly evident at urine concentrations of 500 µg/l, and some of these studies suggest effects down to urine values of 100 µg/l (Miller et al., 1975; Roels et al., 1982). Using the conversion factor discussed in Section 6.3.1.1, urine values of 500 and 100 µg/l would correspond to time-weighted average air concentrations, as measured by static sampler, of 0.05 to 0.20 mg Hg/m^3, respectively. These studies taken as a whole do not identify a threshold urine value below which there are no effects on psychomotor function.

Short-term measurements of total mercury in spot urine samples may not be adequate to identify a threshold for effects on psychomotor function. More studies are needed where time-weighted air and urinary concentrations are used as these indicators may give a better estimate of mercury exposure and, therefore, a better estimate of levels of mercury in the nervous system.

6.3.1.2.2 Effects on kidney function. Buchet et al. (1980) have described dose-response relationships for preclinical effects of mercury on kidney function. Their study group consisted of 63 workers from two chlor-alkali plants. The control group (88 workers) was judged by the plant physician to have no occupational exposure to mercury and to have urinary excretion of mercury and other toxic metals (Cd and Pb) in the normal range of a non-exposed population (mercury in urine less than 5 µg Hg/g creatinine). A broad range of clinical chemistry tests were performed on whole blood, plasma and urine to assure similarity between the exposed and control groups. The groups were similar with regard to age distribution and smoking habits. Alcohol consumption was not mentioned. The effects of mercury on kidney function were followed by measurement of a number of specific proteins in urine--total protein, albumin, transferrin, IgG, β2-microglobulin and β-galactosidase. Abnormal excretion was defined as that exceeding the upper 95-percent limit calculated from the control group. The prevalence of abnormal urinary excretion rates did not relate well with the blood concentrations of mercury, but the excretion of high molecular proteins did correlate with urinary mercury levels. This relationship is depicted in Figure 6-6. The figure indicates that the frequency of abnormal values of the high-molecular-weight protein (albumin) increased with urine mercury concentrations above the background frequency when urinary mercury excretion rose above 10-50 μg Hg/g creatinine. In contrast, no effects were seen in the excretion of the low-molecular-weight protein, β2-microglobulin. Considering all the proteins that were measured, the results of Buchet et al. (Figure 6-7) suggest that a detectable mercury effect can be seen at urinary excretion rates exceeding 50 μg Hg/g creatinine. However, it should be noted that Stonard et al. (1983) were unable to confirm effects on albumin.

Roels et al. (1982) performed a similar study on 102 workers divided equally into control and mercury vapor-exposed subjects. Again, the authors found no effect on the excretion of low-molecular-weight proteins (β2-microglobulin). No statistically significant effect was seen on urinary excretion of albumin, but excretion of total protein was significantly affected. The median urinary concentration for the mercury-exposed group was 71 μg Hg/g creatinine and the upper 95 percentile level was 245 μg Hg/g creatinine. The authors concluded that these findings were "in satisfactory agreement with those previously reported" by Buchet et al. (1980). However, if anything, the second study casts some doubt on the conclusion that effects were occurring at urinary excretion rates as low as 50 μg Hg/g creatinine.

6.3.1.2.3 Other effects. Preclinical biochemical changes have been reported in a study of 81 subjects exposed to mercury vapor in a chlor-alkali plant (Foa et al., 1976). The airborne mercury concentrations were in the range of 0.06 to 0.3 mg Hg/m^3. A number of lysosomal enzymes -- β-galactosidase, β-glucosamidase, acetyl glucosamidase and β-glucosidase--were determined in plasma. Workers in the highest exposed group (N=5, mean urinary mercury 158 μg/l) had significant elevations of three of these lysosomal enzymes. Only β-glucosidase activity was unaffected. The same group of workers was subdivided into four groups based on an index of integrated exposure (duration and intensity). Highly statistically significant correlations were seen in these four subgroups with regard to elevation of plasma lysosomal enzyme activity and the integrated exposure index.

In a more recent study, Stonard et al. (1983) noted that abnormally high urinary levels of two enzymes, N-acetyl-glucosaminidase and gama-glutamyl

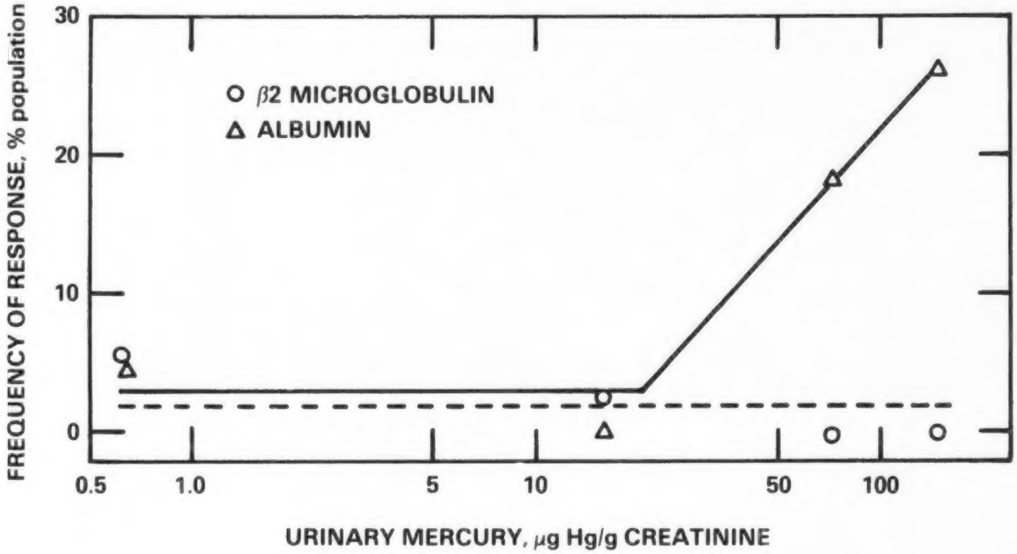

Figure 6-6. Relationship between the percentage of abnormally high urinary concentrations of (○)β_2 microglobulin and (Δ) albumin and average urinary excretion of mercury in 63 workers in two chloralkali plants and in 88 "control" workers. The "controls" were judged not to have occupational exposure to mercury vapor and the urinary excretion of mercury was less than 5 μg Hg/g creatinine. The straight lines were drawn according to hockey stick analysis.

Source: Buchet et al. (1980).

MERCURY IN URINE (μ/g CREATININE)

	<5	5-49.9	50-99.9	>100
NUMBER OF WORKERS	88	37	11	15
Hg-U ($\overline{X}$, μg/g creat)	1.4	19.8	73.2	145.5
Cd-U ($\overline{X}$, μg/g creat)	0.9	0.9	0.9	1.1
Pb-U ($\overline{X}$, μg/g creat)	13.3	9.5	8.4	7.4
Hg-B ($\overline{X}$, μg/100 ml)	1.7	2.2	3.3	4.2
Cd-B ($\overline{X}$, μg/100 ml)	0.23	0.14	0.17	0.16
Pb-B ($\overline{X}$, μg/100 ml)	16.4	14.7	16.7	14.9

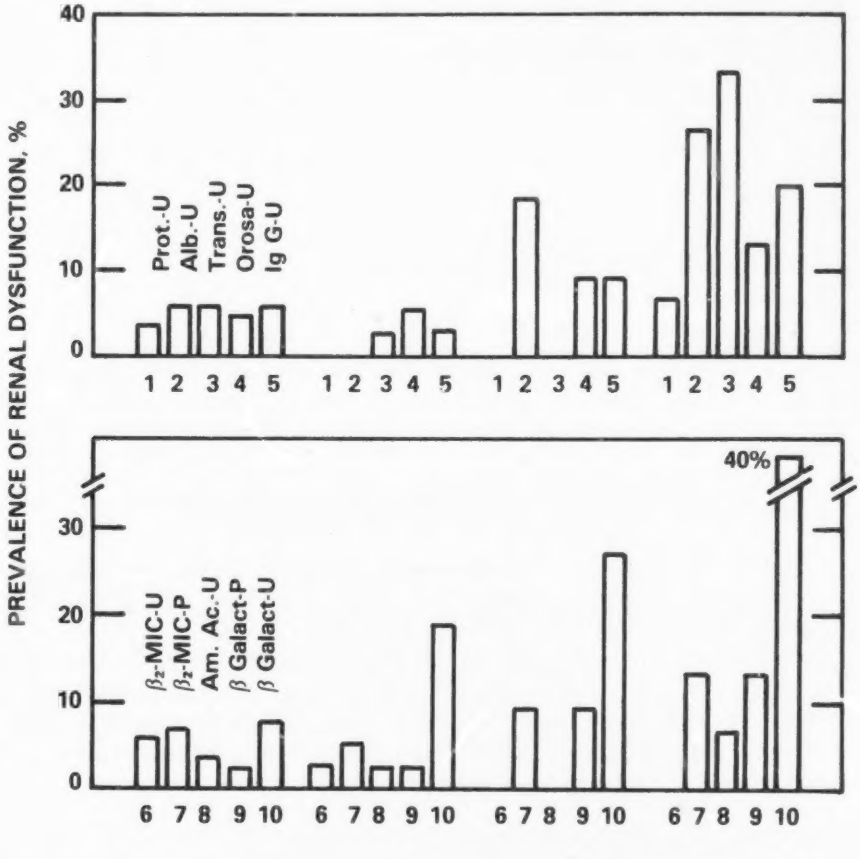

Figure 6-7. Relationship between mercury concentration in urine and the prevalence of signs of renal dysfunction. The parameters are as follows; (1) total proteinuria (Prot-U), (2) albumin-U (Alb-U), (3) transferrin-U (Trans-U), (4) orosomucoid-U (Oroso-U), (5) IgG-U, (6) β_2-microglobulin-U (β_2-microglobulin (β_2-mic-U), (7) plasma $_2$-microglobulin (β_2-mic-P), (8) plasma creatinine (Creat-P), (9) alkaline phosphatase-U (AP-U), (10) β-galactosidaso-U (β-galact-U).

Source: Buchet et al. (1980).

transferase, become evident when urinary mercury exceeded 100 μg Hg/g creatinine.

6.3.1.2.4 Critique and summary. The studies reviewed above have attempted to relate medical and preclinical findings to various measures of exposure and dose, e.g., time-weighted average air concentrations or concentrations of mercury in samples of blood or urine. As mentioned in Section 6.3.1.1, average mercury concentrations in the working area may not represent true exposure because the actual concentration inhaled may be affected by the workers' "microenvironment," such as contaminated clothing and cigarette smoking, transient exposures, or high concentrations of vapor in some phases of the working activities. Intake of mercury vapor will be affected by changes in lung ventilation rates.

Concentrations of mercury in samples of blood and urine may be of value on a group basis for workers having long-term exposures. However, the relative contributions of recent exposures to blood and urine concentrations compared to the release of stored mercury in tissues resulting from earlier exposures is not well understood.

Table 6-4 summarizes the information presented in Section 6.3.1.1 giving a rough indication of the relationship between mercury exposure and health effects. Objective tremors and probably other effects of mercury vapor are likely to occur at air concentrations in excess of 250 $\mu g/m^3$, equivalent to steady-state urinary values in the range of 750-1500 μg Hg/g creatinine. Tremors, perhaps of less intensity and at lower prevalence, have occurred in groups of workers exposed to air concentrations in the range of 100 to 250 $\mu g/m^3$. Below 100 $\mu g/m^3$, the medical effects and their prevalence are less well established. Probably non-specific symptoms are elevated above background prevalence. No threshold air concentration and concentration in urine or blood have been identified. A number of studies have raised the possibility of preclinical effects at air concentrations below 50 $\mu g/m^3$. The clinical significance of the findings of these studies is not fully evident. They do raise the question as to which organ is first affected by mercury; the evidence of high-molecular-weight proteins in urine suggest that glomerular function may be first to be affected. Also, it is of interest that the finding of elevated lysosomal enzyme activity in plasma is consistent with several experimental studies on a variety of mercury compounds (Verity and Reith, 1967; Norseth, 1967, 1969; Coonrod and Peterson, 1969; Norseth and Brendeford, 1971;

Fowler, 1972; Lauwerys and Buchet, 1972). The tissue origin of these enzymes is not known.

6.3.1.3 Factors Affecting the Dose-response Relationship--The dose-effect relationships summarized in Table 6-4 are believed to apply to the general population. However, the occurrence of nephrotic syndrome in a small fraction of similarly exposed workers and experimental evidence indicating an immunological mechanism operative in certain strains of rats suggest a genetic susceptibility in certain individuals. Experiments on rats suggest that susceptible individuals may be identified by examination of characteristics of the histocompatibility complex.

TABLE 6-4. A SUMMARY OF THE RELATIONSHIP BETWEEN OBSERVED EFFECTS AND THE CONCENTRATION OF MERCURY IN AIR AND URINE

		Mercury levels	
Observed effects	Frequency of effect	Air[a] μg/m^3	Urine μg/g creatinine or μg/l[b]
Objective tremor	High	250-500	750-1500
Objective tremor and psychomotor tests	Low	100	300[b]
Non-specific symptoms	Low	50	150[b]
Preclinical plasma lysosomal enzymes		50c	150[d]
Urinary proteins	Low	15-30[c]	50-100

[a] The air concentrations measured by static air samplers are assumed to be a time-weighted average assuming 40 hrs/week exposure.

[b] Calculated from the air concentrations as described in Section 6.3.1.1.

[c] Calculated from the urine value as described in Section 6.3.1.1. These air concentrations would be time-weighted average values over sufficient periods of time to allow urinary excretion rates to attain 50 to 100 μg/gm creatinine.

[d] Information on frequency is not available but the statistical significance of the effect was high (Foa et al., 1976).

The relative sensitivity of different stages of the life cycle to mercury vapor is not known. The developing mammal is not protected from exposure to mercury vapor *in utero*. Studies reviewed in Section 4.1 indicate that mercury vapor readily crosses the placenta to be deposited in fetal tissues. Inhaled mercury vapor may also lead to secretion of inorganic mercury in milk. Health effect studies are incomplete with regard to prenatal exposure and exposure through suckling milk (for discussion see Chapter 5).

Ethanol is known to affect the metabolism of inhaled mercury vapor (for review, see Section 4.1.4.1). No reports are available on studies in animals or humans which demonstrate the influence of ethanol on the toxicity of inhaled mercury vapor. Based on the clinical evidence, Hamilton (1925) stated that alcoholism greatly favors the development of mercurial tremor and that no real abstainer has ever suffered from tremor in a severe form.

Many experimental studies have indicated a protective action of selenium on the toxicity of various forms of mercury including inorganic mercury. Unfortunately, no studies have been reported on interactions between selenium and inhaled mercury vapor. Autopsy observations on mercury miners in Idria, Yugoslavia, have found a correlation between mercury and selenium in tissues, including the brain (Kostial et al., 1975).

Mercury is excreted in the sweat of workers exposed to mercury vapor (Lovejoy et al., 1974). Anecdotal reports in the early literature claim that profuse sweating may alleviate the symptoms of mercury vapor exposure. It is, therefore, at least theoretically possible that temperature, humidity, physical exertion and other factors that influence perspiration may also affect dose-response relationships.

Even though there has been little work done on the relation of diet to mercury exposure effects, dietary factors may be important. Theoretically, a deficiency in sulfur-containing amino acids would interfere with synthesis of thioneine, one of the proteins to which mercury is bound. Drinking milk (a good source of sulfur-containing amino acids) during the work shift was believed to reduce the effects of exposure to mercury by some chlor-alkali workers (Henderson, personal communication).

6.3.2. Compounds of Inorganic Mercury

The effects of inorganic compounds of mercury arise mainly through oral intake, especially in cases of acrodynia due to mercurous salts. The acute lethal dose of mercuric compounds is believed to be 1 to 4 grams in adult subjects (Gleason et al., 1957). Long-term dose-effect relationships for this class of mercury compounds are not known. Chronic oral ingestion of 250 mg Hg_2Cl_2 results in adverse effects on the functions of both the nervous system and kidneys.

Acrodynia appears to be an idiosyncratic response to inorganic mercury. In children who are sensitive to contracting the syndrome, effects have been seen at urinary concentrations as low as 50 µg Hg/l (Warkany and Hubbard, 1948). According to Cheek (1980), roughly one in one thousand infants develops acrodynia if exposed to inorganic mercury.

6.3.3 Methyl Mercury Compounds

6.3.3.1 Indices of Exposure--Blood and strands of head hair are indicator media of choice for individuals suspected of exposure to methyl mercury compounds. In the study sponsored by the World Health Organization, Goldwater (1972) summarized the results of analysis of 812 blood samples obtained from non-exposed individuals in the same 15 countries used for the study of normal urine values (see Section 6.3.1.1). The concentration of total mercury in samples of whole blood were less than the detectable limit (0.5 µg Hg/l) in 77 percent, less than 1 µg Hg/l in 85 percent, and less than 3 µg Hg/l in 95 percent of all the samples. However, it should be noted that the concentration of total mercury in blood is usually influenced by an individual's fish intake as fish and fish products are a dominant source of methyl mercury in the diet. For example, in a study of 41 dieters eating tuna and swordfish, it was reported that 25 percent of the group had average blood levels of 17 µg Hg/l and the highest blood level was in excess of 50 µg Hg/l (McDuffie, 1973). Individuals living in areas almost totally dependent on large carnivorous fish as the major source of protein may have blood levels in excess of 200 µg Hg/l (Turner et al., 1980).

As discussed in Chapter 4, methyl mercury is incorporated into human hair and its concentration in hair is proportional to the concentration of methyl mercury in blood at the time of formation of the hair. Concentrations of mercury along the length of a hair strand reflect past blood levels of methyl mercury -- one centimeter of hair corresponds to one month's growth and, therefore, the mercury concentration in one centimeter indicates the average blood concentration for that month.

This aspect of mercury accumulation in hair must be taken into account when evaluating the numerous reports of mercury concentration in hair (U.S. Environmental Protection Agency, 1979). Some authors report mercury concentration for a specified length of hair, others for the entire length of the hair strand. The situation is further complicated, as is the case of other metals, by the possibility of external contamination and by the vagaries of different washing procedures. A World Health Organization study reported a mean level of total mercury in hair of 1 μg Hg/g (standard error = 0.4) in 963 individuals in rural Iraq who had no known exposure to mercury and had low or no fish consumption (Kazantzis et al., 1976). These findings agree with a study on "normal" individuals in Canada having low fish consumptions (Perkons and Jervis, 1966) and with a study of 119 males in the U.S. Navy (Gordus et al., 1974). In both these studies, the average mercury concentrations in hair were 1.5 μg Hg/g (range, 1.0 to 3.0 μg Hg/g) and 1.9 μg Hg/g (range not given), respectively. Hair levels in normal subjects in Japan appear to be generally higher than those in the United States with mean values of approximately 4 μg Hg/g (Yamaguchi and Matsumoto, 1968). As in the case of blood concentrations, fish intake has an important influence on hair concentrations of mercury. Individuals having unusually high dietary intakes of fish or marine mammals may exceed values of 50 μg Hg/g in hair (Wheatley, 1979).

6.3.3.2 Effects and Dose-response Relationships--The effects of methyl mercury compounds arise primarily through oral ingestion of contaminated fish or bread, although a few cases of methyl mercury industrial poisoning have probably been due to inhalation and skin absorption. Skin absorption, as a possible route of methyl mercury exposure, has been noted in cases where methyl mercury was used to treat fungal infections of the skin (WHO, 1976). Signs and symptoms of methyl mercury poisoning are not affected by the route of intake, but characterizations of dose-effect and dose-response relationships are available only for oral exposures to adults and transplacental passage to the fetus.

Dose-effect and dose-response relationships for methyl mercury compounds in man have been presented and evaluated previously (Bakir et al., 1973; World Health Organization, 1976, 1980; Nordberg, 1976; U.S. Environmental Protection Agency, 1980). The WHO Expert Group (World Health Organization, 1976, 1980) concluded that a low prevalence (about 5 percent) of the population could present with the earliest symptom of methyl mercury poisoning (paresthesia) at blood concentrations of methyl mercury in the range of 0.2 to 0.5 µg/1, corresponding to hair concentrations in the range of 50 to 125 µg/g or to long-term daily intakes of methyl mercury between 3 to 7 µg/kg body weight. Nordberg and Strangert (1978), in a more recent analysis, calculated the expected prevalence (risk) of paresthesia based on both data relating blood levels to frequency of paresthesia (Bakir et al., 1973) and data relating daily intake to blood levels (Al-Shahristani and Shihab, 1974). For human adults, it was calculated that a long-term daily intake of 200 µg Hg as methyl mercury (approximately 3-4 µg/kg body weight) would give rise to a risk of about 8 percent for symptoms of paresthesia. It was also calculated that a daily intake of 50 µg/Hg as methyl mercury would give rise to a risk of about 0.3 percent, assuming that the threshold, if it exists, lies below this daily intake.

Both epidemiological and experimental observations indicate that prenatal life is the most sensitive stage of the life cycle to methyl mercury exposure. Dose-response and dose-effect relationships have been published for the earliest (mildest) effects arising from prenatal exposure (Marsh et al., 1980, 1981; Clarkson et al., 1980; Berlin, 1983). These data are still under evaluation, but preliminary reports indicate that prenatal life is about three to four times more sensitive than are adults.

6.3.4 Other Mercury Compounds

Phenylmercury compounds belong to a broad chemical class of aryl and alkoxyaryl mercurials which have worldwide use as fungicides, contraceptive spermicides, and disinfectants. Despite the fact that human exposure has been extensive in the agricultural, paint, and pharmaceutical industries, quantitative information on dose-effect relationships such as reported for mercury vapor (Smith et al., 1970; Buchet et al., 1980) and methyl mercury (Bakir et al., 1973) has not been reported for this important class of organic compounds.

Goldwater (1973) found no evidence of toxicity in 13 workers employed for 11 to 23 years in the manufacture of phenylmercury. Exposure levels were not reported, but urinary concentrations of mercury varied from 85 to 100 µg/l. Cotter (1947) found liver damage in ten subjects exposed to phenylmercury salts, but other substances may have been involved in the exposure. Renal damage and intestinal complaints have been reported (Skerfving and Vostal, 1972). In general, there seems to be no difference in the toxicity of various phenylmercurials which have been studied. The symptoms, where noted, have resembled those of inorganic mercury. According to clinical evidence (Biskind, 1933), phenylmercury compounds, when applied topographically to the skin, can produce signs of toxicity. Delayed-type hypersensitivity has been reported from skin contact with phenylmercury compounds (Mathews, 1968).

Phenylmercury acetate was widely used as a spermicidal contraceptive administered vaginally in a gel. Enhanced urinary excretion of mercury was believed to result from the vaginal absorption of phenylmercury, but no adverse health effects have been reported from use of the contraceptive (Goldwater, 1973).

6.4 POPULATIONS AT RISK

With regard to the direct health effects of inhaled mercury vapor, the special groups at risk are those occupationally exposed. Exposure, therefore, to the adult human is in the workplace. Some of the people exposed are women of childbearing age. The effect of prenatal exposures and exposure during the suckling period has not been adequately investigated. Of special interest is the group of female dental assistants exposed to mercury vapor through the use of dental amalgams containing metallic mercury in dental fillings. An unknown number of women of childbearing age are also exposed to mercury vapor in such industries as thermometer manufacturing and industries where the calibration of pipettes and the manufacture of other scientific instruments involves the use of liquid metallic mercury. One report in the foreign literature (Mishonova et al., 1980) reported effects on pregnancy and parturition in women occupationally exposed to mercury vapor; insufficient detail was available to evaluate dose-response relationships.

Homes of people occupationally exposed to mercury vapor may be liable to contamination. This aspect of occupational exposure in industries using liquid metallic mercury has not been well explored, but at least one report in the literature (Danzinger and Possick, 1973) indicates that contamination of the home can occur.

Specific segments of the general public may be at risk from methyl mercury compounds especially pregnant women, small children, and those who commonly consume two or more times the national average of 15 pounds of fish per year.

As discussed in Chapter 5, it is at least theoretically possible that exposures to both methyl mercury compounds and to mercury vapor may have additive effects on the central nervous system. Epidemiological surveys have not yet been made to assess the probability of combined exposures to methyl mercury in fish and seafood and the occupational exposure to mercury in women of childbearing age. It would be highly desirable for the U.S. Environmental Protection Agency and the Food and Drug Administration to coordinate their efforts to determine the population(s) and relative degree of risk.

6.5 SUMMARY

Atmospheric mercury accounts for all the mercury vapor and approximately 2 percent of the methyl mercury retained each day. The diet, mainly fish and fish products, accounts for most, 98 percent, of the daily retention of methyl mercury. The diet also accounts for virtually all of the intake of inorganic mercury compounds.

Time-weighted air concentrations are the usual means of assessing human exposure to mercury vapor. Urine is the most frequently used indicator medium to assess body burden after chronic exposure to mercury vapor. Long-term exposure to 100 µg Hg/m^3, when measured by static samplers, is roughly equivalent to a urine concentration of 300 µg Hg/l. However, when measured by personal samplers, 100 µg Hg/m^3 is equivalent to about 100 µg Hg/l of urine. Approximately 95 percent of all urine samples are below 20 µg Hg/l in people who have had no known exposure to mercury. Mild proteinuria may occur in the most sensitive adults at urine values between 50 and 100 µg Hg/l following chronic occupational exposures. Objective tremor and psychomotor disturbances appear in sensitive individuals usually at urine values above 300 µg/l, but no clear threshold has been established. The effects of mercury vapor usually disappear within a few months after cessation of exposure. Despite the fact that inhaled mercury vapor crosses the placenta, little information has been published on the consequences of prenatal and perinatal exposures.

Blood and head hair are the most commonly used indicator media for body burden of mercury after exposure to methyl mercury compounds. Levels of methyl mercury in these media are influenced by fish consumption. For average persons with low level fish consumption, approximately 95 percent have blood levels below 3 µg Hg/l and average hair values usually less than 2 µg Hg/g. In individuals having unusually high fish intake, such as "weight watchers" eating tuna and swordfish, blood levels may exceed 50 µg Hg/l. In the most sensitive adults, the mild effects of methyl mercury, such as paresthesia, may appear at blood levels of 200 µg Hg/l, which is equivalent to hair levels of 50 µg Hg/gm. More severe effects, such as constricted visual field and ataxia, appear at blood levels above 500 to 1000 μg Hg/l, equivalent to hair levels of 125 to 250 μg Hg/g. The severe effects are irreversible; paresthesia may or may not be irreversible.

Prenatal life is the most sensitive stage of the life cycle to methyl mercury with the milder effects, such as psychomotor retardation, being associated with maternal hair levels during pregnancy in the vicinity of 10-20 μg Hg/gm. The most severe effects associated with maternal blood levels in excess of 100 μg Hg/l are cerebral palsy and microcephaly. All prenatal effects to date have been found to be irreversible.

Possible effects due to chronic exposure to compounds of inorganic mercury have been rarely reported. Occupational exposure to aerosols of mercuric oxide may lead to signs and symptoms similar to the syndrome of amyotrophic lateral sclerosis. These manifestations of mercuric oxide exposure are reversible upon cessation. Dose-effect relationships have not been reported, but air concentrations associated with these effects are probably higher than those associated with the earliest effects of mercury vapor.

Dose-effect relationships for phenylmercury compounds have not been reported in humans. Occupational experience suggests that the human inhalation toxicity of this class of organomercurials is less than that of mercury vapor. Dietary intake studies in rodents yields evidence that these compounds are better absorbed than inorganic mercury compounds and that the kidney is the target organ as in the case of inorganic mercury. There is need for quantitative dose-response data in humans on this class of organomercurials.

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